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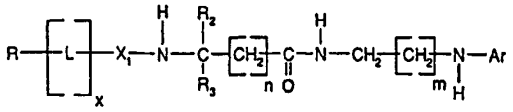

(I)

(57) Abstract

The invention provides aminoacid–arylaminoalkylamides in which the C–terminal carboxy group of the amino acid is substituted by an arylaminoalkylamino substituent and in which the amino nitrogen atom of the amino acid forms a peptide or pseudopeptide linkage which optionally additionally comprises a –methylene–hetero atom– linker or an additional hetero atom, through which it is directly substituted by aryl, lower alkyl, lower alkenyl, lower alkynyl or heterocyclyl, or a physiologically–acceptable and –cleavable ester of a salt thereof; in particular compounds of formula (I), or a physiologically–acceptable and –cleavable ester or a salt thereof, wherein the symbols are as defined, as cathepsin K inhibitors for use pharmaceutically for therapeutic or prophylactic treatment of diseases or medical conditions in which cathepsin K is implicated.

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ARYLAMINOALKYLAMIDES

This invention relates to inhibitors of cysteine proteinases, in particular to arylaminoalkylamide cathepsin K inhibitors and to their pharmaceutical use for the treatment or prophylaxis of diseases or medical conditions in which cathepsin K is implicated.

Cathepsin K is a member of the family of lysosomal cysteine cathepsin enzymes, e.g. cathepsins B, K, L and S, which are implicated in various disorders including inflammation, rheumatoid arthritis, osteoarthritis, osteoporosis, tumors (especially tumor invasion and tumor metastasis), coronary disease, atherosclerosis (including atherosclerotic plaque rupture and destabilization), autoimmune diseases, respiratory diseases, infectious diseases and immunologically mediated diseases (including transplant rejection).

In accordance with the invention it has been found that particular arylaminoalkylamides are useful as cathepsin K inhibitors and can be used for the treatment of the above-cited cysteine cathepsin dependent conditions.

Accordingly the present invention provides an aminoacid-arylaminoalkylamide in which the C-terminal carboxy group of the amino acid is substituted by an arylaminoalkylamino substituent and in which the amino nitrogen atom of the amino acid forms a peptide or pseudopeptide linkage which optionally additionally comprises a -methylene-hetero atom- linker or an additional hetero atom, through which it is directly substituted by aryl, lower alkyl, lower alkenyl, lower alkynyl or heterocyclyl, or a physiologically-acceptable and -cleavable ester or a salt thereof.

The invention also provides an aminoacid-arylaminoalkylamide as defined above, for use as a pharmaceutical.

The invention further provides a pharmaceutical composition comprising an aminoacid-arylaminoalkylamide as defined above as an active ingredient.

The invention yet further provides a method of treating a patient suffering from or susceptible to a disease or medical condition in which cathepsin K is implicated, comprising administering an effective amount of an aminoacid-arylaminoalkylamide as defined above to the patient.

The invention further includes the use of an aminoacid-arylaminoalkylamide as defined above for the preparation of a medicament for therapeutic or prophylactic treatment of a disease or medical condition in which cathepsin K is implicated.

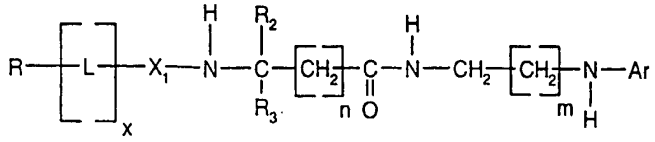
The amino acid residue of the aminoacid-arylaminoalkylamides of the invention may be a β-amino acid residue and is preferably an α-amino acid residue, including both natural and unnatural α-amino acid residues. Herein the "natural α-amino acid residues" denotes the 20 amino acids obtainable by translation of RNA according to the genetic code or the corresponding amides thereof, as appropriate. "Unnatural α-amino acid residues" are α-amino acids which have α-substituents other than those found in "natural α-amino acid residues". Preferred α-amino acid residues are 1-amino-cyclohexanecarboxylic acid, 1-amino-cycloheptanecarboxylic acid, 2-amino-norbornan-2-carboxylic acid, 2-amino-2-ethyl-butanoic acid, phenylalanine, histidine, tryptophan and leucine and derivatives thereof, e.g. as hereinafter described. Preferred β-amino acid residues are those having side chains corresponding to those of the preferred α-amino acid residues.

The aryl, lower alkyl, lower alkenyl, lower alkynyl or heterocyclyl substituent (hereinafter referred to as R) is attached to the the N-terminal nitrogen atom of the dipeptide via a peptide linkage, i.e. as R-C(O)-NH-, or via a pseudopeptide linkage. Suitable pseudopeptide linkages include sulphur in place of oxygen and sulphur and phosporous in place of carbon, e.g. as R-C(S)-NH-, R-S(O)-NH-, R-$S(O)_2$-NH- or R-$P(O)_2$-NH and analogues thereof. Additionally the peptide or pseudopeptide linkage between the R substituent and the N-terminal nitrogen atom may comprise an additional hetero atom, e.g. as R-Het-C(O)-NH-, or a -methylene-hetero atom- linker, e.g. as R-Het-CH_2-C(O)-NH- or R-CH_2-Het-C(O)-NH-, wherein Het is a hetero atom selected from O, N or S, and pseudopeptide containing alternatives thereof, e.g. as defined above. When the linkage between the aryl substituent and the N-terminal nitrogen atom comprises a -methylene-hetero atom- linker, the methylene group and the hetero atom may be optionally further substituted, e.g. as hereinafter described.

The R substituent may be further substituted, e.g. by up to 5 substituents independently selected from halogen, hydroxy, amino, nitro, optionally substituted C_{1-4}alkyl (e.g. alkyl substituted by hydroxy, alkyloxy, amino, optionally substituted alkylamino, optionally substituted dialkylamino, aryl or heterocyclyl), C_{1-4}alkoxy, C_{2-6}alkenyl, CN, trifluoromethyl, trifluoromethoxy, aryl, (e.g.phenyl or phenyl substituted by CN, CF_3, halogen, C_{1-4}alkoxy, C_{1-6}alkyl), aryloxy, (e.g. phenoxy or phenoxy substituted by CN, CF_3, halogen, OCH_3), aryloxy (e.g. benzyloxy), optionally substituted carbonyl (e.g. alkylcarbonyl, alkoxycarbonyl or arylcarbonyl) or an optionally substitued heterocyclic residue.

The alkyl moiety of the aminoacid-arylaminoalkylamides of the invention is typically lower alkylene, preferably C_2 to C_6 lower alkylene, especially ethylene (i.e. $-CH_2-CH_2-$).

Accordingly in preferred embodiments the invention provides a compound of formula I, or a physiologically-acceptable and -cleavable ester or a salt thereof



I

wherein:

R is optionally substituted (aryl, lower alkyl, lower alkenyl, lower alkynyl, or heterocyclyl);

R_2 and R_3 are independently hydrogen, or optionally substitued [lower alkyl, cycloalkyl, bicycloalkyl, or (aryl, biaryl, cycloalkyl or bicycloalkyl)-lower alkyl]; or

R_2 and R_3 together represent lower alkylene, optionally interrupted by O, S or NR_6, so as to form a ring with the carbon atom to which they are attached

wherein R_6 is hydrogen, lower alkyl or aryl-lower alkyl; or

either R_2 or R_3 are linked by lower alkylene to the adjacent nitrogen to form a ring;

Ar is optionally substituted aryl;

X_1 is $-C(O)-$, $-C(S)-$, $-S(O)-$, $-S(O)_2-$, $-P(O)(OR_6)-$

wherein R_6 is as defined above;

L is optionally substituted -Het-, $-Het-CH_2-$ or $-CH_2-Het-$,

wherein Het is a hetero atom selected from O, N or S;

n is 0 or 1;

m is 1, 2, 3, 4 or 5;

x is 0 or 1.

Above and elsewhere in the present description aryl denotes both carbocyclic and heterocyclic aryl.

In formula I, R, R_2, R_3, Ar and L may be further substituted by one or more, e.g. up to 5, substituents independently selected from lower alkyl, aryl, aryl-lower alkyl, cycloalkyl, heterocyclyl, -CN, -halogen, -OH, $-NO_2$, $-NR_9R_{10}$, -lower alkyl-NR_9R_{10}, $-X_3-R_7$, -lower alkyl-X_3-R_8, halo-substituted lower alkyl-,

wherein R_7 is optionally substituted (lower alkyl, aryl, aryl-lower alkyl, cycloalkyl, bicycloalkyl or heterocyclyl), and

R_8 is H, or optionally substituted (lower alkyl, aryl, aryl-lower alkyl, cycloalkyl, bicycloalkyl or heterocyclyl),

X_3 is -O-, -S-, $-NR_8-$, -C(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, -C(O)O-, -C(S)O-, $-C(O)NR_8-$, or $-CH_2-$

wherein R_8 is as defined above,

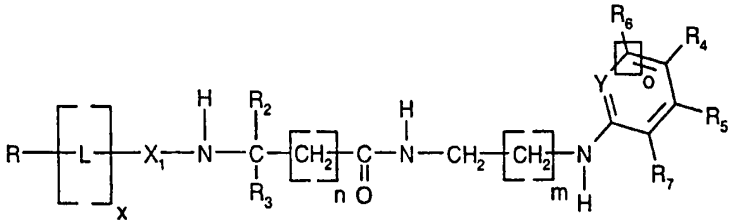
R_9 and R_{10} are independently as defined above for R_8, or $-X_4-R_8$,

wherein X_4 is -C(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, -C(O)O-, -C(S)O-, $-C(O)NR_6-$

wherein R_6 is as defined above, or

R_9 and R_{10} together with N form a heteroaryl group or a saturated or unsaturated heterocycloalkyl group, optionally containing one or more additional heteroatoms selected from O, N or S.

Conveniently Ar comprises an aryl or hetero aryl ring comprising from 5 to 8 ring atoms one of which may be may be a hetero atom, e.g. O, N or S, optionally substituted, e.g. by up to 3 substituents, for instance to provide a compound of formula II, or a physiologically-acceptable and -cleavable ester or a salt thereof



II

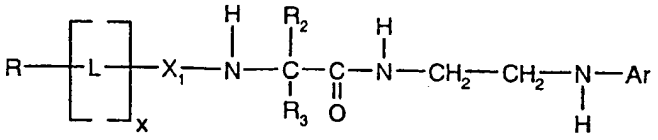
wherein R, R_2, R_3, L, X_1, x, n and m are as defined and

R_4, R_5, R_6 and R_7 independently are H, lower alkyl (e.g. methyl), lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy), aryl-lower alkoxy (e.g. -O-benzyl), cycloalkoxy, cycloalkyl-lower alkoxy (e.g. cycloalkylmethoxy), heterocyclyloxy, heterocyclyl-lower alkoxy, halogen, e.g. Cl, Br or F, or trifluoromethyl

Y is -CH- or a heteroatom selected from O, N or S, and

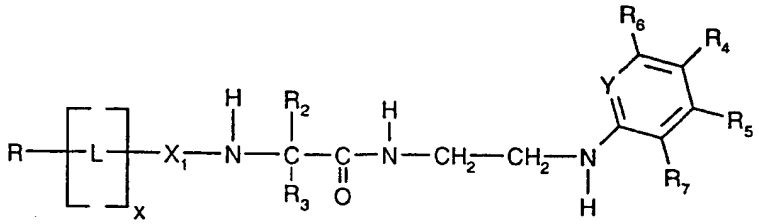
o is 0,1,2 or 3.

In preferred embodiments of the compounds of formulae I and II, n is 0 and/or m is 1 and/or o is 1, for instance to provide compounds of formulae I' and II', or physiologically-acceptable and -cleavable esters or salts thereof



I'

or



II'

wherein the symbols have the meanings defined above.

The substituents of the compounds of formulae I, I', II and II' have the following preferred significances. Preferred compounds of formulae I, I', II and II'comprise compounds having preferred substituents, singly or in any combination.

Preferably when R comprises aryl, the aryl is optionally substituted (phenyl, naphthyl, phenanthrenyl, thiophenyl, furanyl, pyrrolyl, pyrazolyl, thiazolyl, pyridinyl, indolyl, quinolinyl, isoquinolinyl, benzothienyl and benzofuranyl).

Preferably R_2 is hydrogen.

Preferably R_3 is optionally substituted (lower alkyl, aryl-lower alkyl or cycloalkyl-lower alkyl), or R_3 and R_2 together with the carbon atom to which they are attached form a C_5-C_8, especially a C_6 or C_7, cycloalkylgroup. More preferably R_3 is $-CH_2-CH(CH_3)_2$, or optionally

substituted benzyl, cyclohexylmethyl, naphthalenylmethyl, indolylmethyl, benzothienylmethyl or benzofuranylmethyl, or R_3 and R_2 together with the carbon atom to which they are attached form a cyclohexane or cycloheptane ring.

Preferably Ar is optionally substituted (phenyl, naphthyl, phenanthrenyl, thiophenyl, furanyl, pyrrolyl, pyrazolyl, thiazolyl, pyridinyl, indolyl, quinolinyl, isoquinolinyl, benzothienyl and benzofuranyl). More preferably Ar is optionally substituted (phenyl, naphthyl, quinolinyl or 1,2,3,5-tetrahydroquinolinyl).

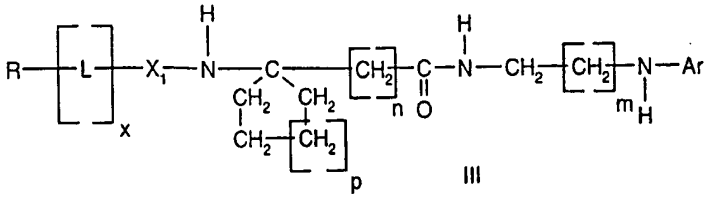
Preferably Y is CH.

Preferably at least one of R_4, R_5, R_6, or R_7 preferably R_4, is lower alkyl (e.g. methyl), lower alkoxy (e.g. methoxy, butoxy, benzyloxy, pentafluorophenylmethoxy), or halo (e.g. chloro or fluoro).

Preferably $-X_1-$ is $-C(O)-$.

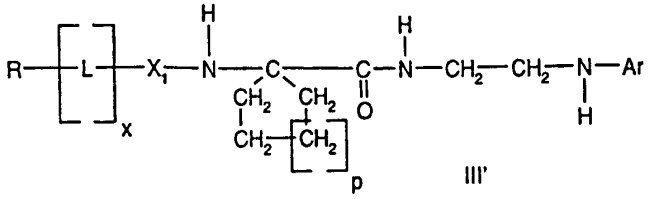
Preferably either x is 0, or when x is 1 L is $-CH_2-O-$.

In particularly preferred embodiments R_3 and R_2 together with the carbon atom to which they are attached form a C_5-C_8, especially a C_6 or C_7, cycloalkyl group (including internally-bridged cycloalkyl groups, e.g. norborane); for instance to provide compounds of formula III



III

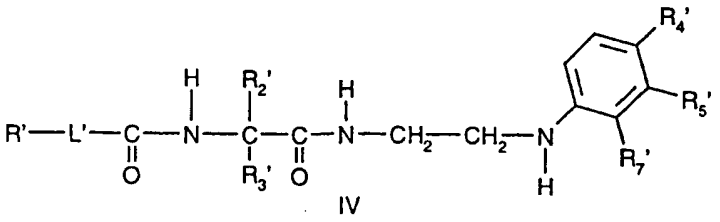
or especially III'



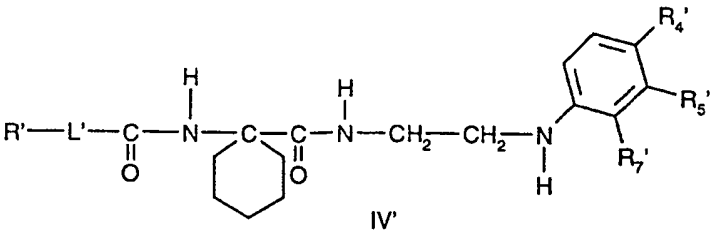
III'

wherein R, L, X_1, Ar, n and m are as defined above and p is 1, 2, 3 or 4; or physiologically-acceptable and -cleavable esters or salts thereof (and compounds in which the cycloalkyl group comprises an internal carbon-carbon bond or lower alkylene, e.g. methylene, bridge).

In further particularly preferred embodiments the invention provides compounds of formulae and IV and IV', or physiologically-acceptable and -cleavable esters or salts thereof



IV



IV'

wherein

R' is optionally substituted (aryl or heterocyclyl);

L' is $-CH_2-O-$, $-CH_2-$, $-OC(R_{14}R_{15})-$ or a direct bond, where R_{14} and R_{15} are independently H or lower alkyl;

R_2' is H and R_3' is lower alkyl or cycloalkyl; and

R_4', R_5' and R_7' are independently H, halogen, aryl-lower alkoxy, lower alkyl, lower alkoxy, cycloalkyloxy, cycloalkyl-lower alkoxy, heterocyclyloxy, heterocyclyl-lower alkoxy or optionally substituted amino-lower alkoxy.

Preferably R_3' is isobutyl, propyl or cyclopentyl.

R' as aryl is preferably phenyl (e.g. optionally substituted, preferably at the 4-position, e.g. by 4-methylpiperazinyl, phenyl, methoxy, isopropoxy, tertiary butoxy, ethyl, isopropyl, imidazolyl, oxazolyl, halogen, methylcarbonyl, diethylamino, pyrazolyl, 1-(2-methoxyethyl)piperidin-4-yl, 1-methyl-3-imidazol-1-ylpropyl and 5-chloropyrid-2-yloxy, 6-methyl-pyridin-3-yloxy, 5-methyl-pyridin-3-ylmethyl, 5-chloro-pyridin-3-yloxy, 5-chloro-pyridin-3-yloxy, or 3-pyrid-3-ylpropyl).

R' as heterocyclyl is preferably piperidinyl (e.g. 4-phenylpiperidin-1-yl), piperazinyl (e.g. 4-methoxypiperazinyl), indole, 1-methylindole or oxindole.

R_4' as halogen is preferably chloro or fluoro.

R_4' as aryl-lower alkoxy is preferably phenyl-lower alkoxy (e.g. benzyloxy, 4-fluorobenzyloxy, pentafluorobenzyloxy), imidazo-lower alkoxy (e.g. 2-imidazol-1-ylethyoxy) or pyridyl-lower alkoxy (e.g. pyrid-4-ylmethyl).

R_4' as lower alkyl is preferably methyl.

R_4' as lower alkoxy is preferably methoxy, isopropoxy, butoxy or isobutoxy.

R_4' as cycloalkyloxy is preferably cyclopentyloxy or cyclohexyloxy.

R_4' as cycloalkyl-lower alkoxy is preferably cyclopentylmethoxy or cyclopropylmethoxy.

R_4' as heterocyclyloxy is preferably, tetrahydropyranoxy, piperidyloxy (e.g. 1-methylpiperid-4-yloxy).

R_4' as heterocyclyl-lower alkoxy is preferably piperidyl-lower alkoxy (e.g. 2-piperid-1-ylethoxy) or morpholino-lower alkoxy (e.g. 2-morpholinoethoxy).

R_4' as optionally substituted amino-lower alkoxy is preferably dimethylaminoethyl.

R_5' is preferably H, lower alkyl (e.g. methyl), lower alkoxy (e.g. methoxy) or halogen.

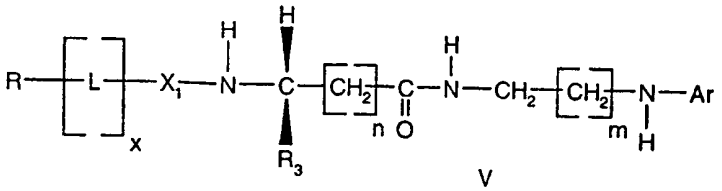
R_7' is preferably H or halogen.

The compounds of formulae I, I', II, II', and IV depending on the nature of substituents, may possess one or more asymmetric carbon atoms. The resulting diastereomers and enantiomers are encompassed by the instant invention. Preferably, however, e.g. for pharmaceutical use in

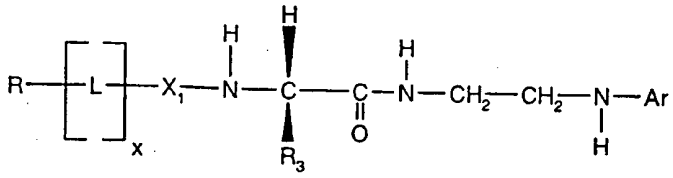
accordance with the invention, the compounds of formulae I, I', II, II' and IV are provided in pure or substantially pure epimeric form, e.g. as compositions in which the compounds are present in a form comprising at least 90%, e.g. preferably at least 95% of a single epimer (i.e. comprising less than 10%, e.g. preferably less than 5% of other epimeric forms).

Preferred compounds of formula I are those wherein the asymmetric carbon atom to which R_2 and/or R_3 are attached corresponds to that of an L-amino acid precursor and is generally assigned the (S)-configuration. Preferred compounds of formula I wherein R_2 represents hydrogen can be represented by formulae V, V', V", V"' and V"", corresponding to preferred compounds of formulae I, I', II, II' and IV respectively.

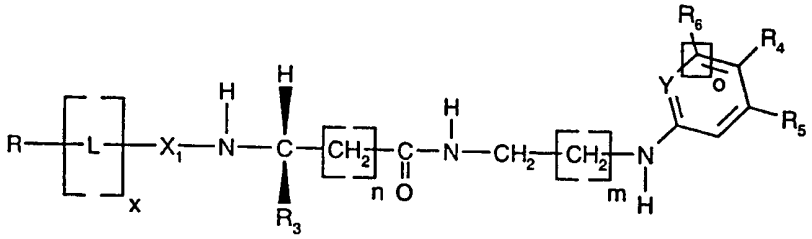
Thus in particularly preferred embodiments the invention provides a compound of formula V, V', V" or V"'



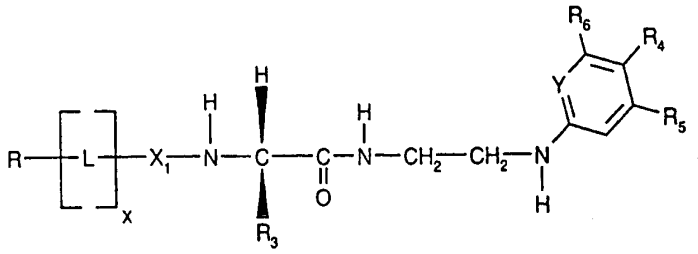
V



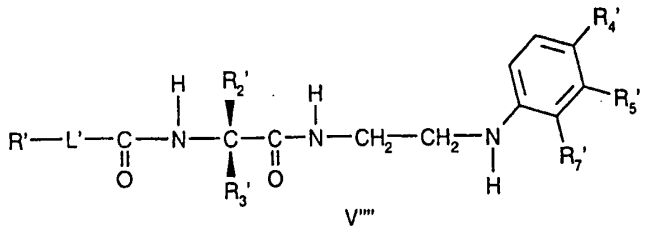
V'



V"



V'''



V''''

wherein the symbols are as defined above, and

physiologically-acceptable and -cleavable esters or salts thereof.

The compounds of formula I, I' II, II',III, III', IV, IV', V, V', V", V''' and V'''' as defined above are hereinafter referred to as Compounds of the Invention.

The general definitions used herein have the following meaning within the scope of the invention, unless otherwise specified.

The term "lower" referred to above and hereinafter in connection with organic radicals or compounds respectively defines a compound or radical which may be branched or unbranched with up to and including 7, preferably up to and including 4 and (as unbranched) one or two carbon atoms.

A lower alkyl group is branched or unbranched and contains 1 to 7 carbon atoms, preferably 1-4 carbon atoms. Lower alkyl represents, for example, methyl, ethyl, propyl, butyl, isopropyl or isobutyl.

Lower alkenyl represents either straight chain or branched alkenyl of 2 to 7 carbon atoms, preferably 2-4 carbon atoms, e.g. as vinyl, propenyl, isopropenyl, butenyl, isobutenyl or butadienyl.

Lower alkynyl represents either straight chain or branched alkynyl of 2 to 7 carbon atoms, preferably 2-4 carbon atoms, e.g. as acetylenyl, propynyl, isopropynyl, butynyl or isobutynyl.

Lower alkyl, lower alkenyl and lower alkynyl may be substituted by up to 3 substituents selected from lower alkoxy, aryl, heterocyclyl, hydroxy, halogen, cyano, optionally substituted amino, optionally substituted amino-oxy- or trifluoromethyl.

Lower alkylene represents either straight chain or branched alkylene of 1 to 7 carbon atoms, i.e. a divalent hydrocarbon radical of 1 to 7 carbon atoms; for instance, straight chain lower alkylene being the bivalent radical of formula $-(CH_2)_n-$, where n is 1, 2, 3, 4, 5, 6 or 7. Preferably lower alkylene represents straight chain alkylene of 1 to 4 carbon atoms, e.g. a methylene, ethylene, propylene or butylene chain, or said methylene, ethylene, propylene or butylene chain mono-substituted by C_1-C_3-alkyl (advantageously methyl) or disubstituted on the same or different carbon atoms by C_1-C_3-alkyl (advantageously methyl), the total number of carbon atoms being up to and including 7.

A lower alkoxy (or alkyloxy) group preferably contains 1-7 carbon atoms, advantageously 1-6 carbon atoms, and represents for example ethoxy, propoxy, isopropoxy, isobutoxy, preferably methoxy. Lower alkoxy includes cycloalkyloxy and cyloalkyl-lower alkyloxy.

Halogen (halo) preferably represents chloro or fluoro but may also be bromo or iodo.

Aryl represents carbocyclic or heterocyclic aryl.

Carbocyclic aryl represents monocyclic, bicyclic or tricyclic aryl, for example phenyl or phenyl mono-, di- or tri-substituted by one, two or three radicals selected from lower alkyl, lower alkoxy, aryl, hydroxy, halogen, cyano, amino, amino-lower alkyl, trifluoromethyl, lower alkylenedioxy and oxy-C_2-C_3-alkylene; all of which are optionally further substituted, for instance as hereinbefore defined; or 1- or 2-naphthyl; or 1- or 2-phenanthrenyl. Lower alkylenedioxy is a divalent substituent attached to two adjacent carbon atoms of phenyl, e.g. methylenedioxy or ethylenedioxy. Oxy-C_2-C_3-alkylene is also a divalent substituent attached to two adjacent carbon atoms of phenyl, e.g. oxyethylene or oxypropylene. An example for oxy-C_2-C_3-alkylene-phenyl is 2,3-dihydrobenzofuran-5-yl.

Preferred as carbocyclic aryl is naphthyl, phenyl or phenyl mono- or disubstituted by lower alkoxy, phenyl, halogen, lower alkyl or trifluoromethyl, especially phenyl or phenyl mono- or disubstituted by lower alkoxy, halogen or trifluoromethyl, and in particular phenyl.

Examples of substituted phenyl groups as R are, e.g. 4-chlorophen-1-yl, 3,4-dichlorophen-1-yl, 4-methoxyphen-1-yl, 4-methylphen-1-yl, 4-aminomethylphen-1-yl, 4-

methoxyethylaminomethylphen-1-yl, 4-hydroxyethylaminomethylphen-1-yl, 4-hydroxyethyl-(methyl)-aminomethylphen-1-yl, 3-aminomethylphen-1-yl, 4-N-acetylaminomethylphen-1-yl, 4-aminophen-1-yl, 3-aminophen-1-yl, 2-aminophen-1-yl, 4-phenyl-phen-1-yl, 4-(imidazol-1-yl)-phen-1-yl, 4-(imidazol-1-ylmethyl)-phen-1-yl, 4-(morpholin-1-yl)-phen-1-yl, 4-(morpholin-1-ylmethyl)-phen-1-yl, 4-(2-methoxyethylaminomethyl)-phen-1-yl and 4-(pyrrolidin-1-ylmethyl)-phen-1-yl, 4-(2-thiophenyl)-phen-1-yl, 4-(3-thiophenyl)-phen-1-yl, 4-(4-methylpiperazin-1-yl)-phen-1-yl, and 4-(piperidinyl)-phenyl and 4-(pyridinyl)-phenyl optionally substituted in the heterocyclic ring.

Heterocyclic aryl represents monocyclic or bicyclic heteroaryl, for example pyridyl, indolyl, quinoxalinyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, benzopyranyl, benzothiopyranyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl, or any said radical substituted, especially mono- or di-substituted, by e.g. lower alkyl, nitro or halogen. Pyridyl represents 2-, 3- or 4-pyridyl, advantageously 2- or 3-pyridyl. Thienyl represents 2- or 3-thienyl. Quinolinyl represents preferably 2-, 3- or 4-quinolinyl. Isoquinolinyl represents preferably 1-, 3- or 4-isoquinolinyl. Benzopyranyl, benzothiopyranyl represent preferably 3-benzopyranyl or 3-benzothiopyranyl, respectively. Thiazolyl represents preferably 2- or 4-thiazolyl, advantageously 4-thiazolyl. Triazolyl is preferably 1-, 2- or 5-(1,2,4-triazolyl). Tetrazolyl is preferably 5-tetrazolyl.

Preferably, heterocyclic aryl is pyridyl, indolyl, quinolinyl, pyrrolyl, thiazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl, or any said radical substituted, especially mono- or di-substituted, by lower alkyl or halogen; and in particular pyridyl.

Biaryl may be carbocyclic biaryl, preferably e.g. biphenyl, namely 2, 3 or 4-biphenyl, advantageously 4-biphenyl, each optionally substituted by e.g. lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano, or heterocyclic-carbocyclic biaryl, preferably e.g. thienylphenyl, pyrrolylphenyl and pyrazolylphenyl.

Cycloalkyl represents a saturated cyclic hydrocarbon optionally substituted by lower alkyl which contains 3 to 10 ring carbons and is advantageously cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl optionally substituted by lower alkyl.

Bicycloalkyl is for example norbornanyl.

Amino may be optionally substituted, e.g. by lower alkyl.

Heterocyclyl represents a saturated cyclic hydrocarbon containing one or more, preferably 1 or 2, hetero atoms selected from O, N or S, and from 3 to 10, preferably 5 to 8, ring atoms; for

example, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyrrolyl, piperidinyl, piperazinyl or morpholino; all of which may be optionally substituted, for instance as hereinbefore defined for carbocyclic aryl.

Aryl-lower alkyl represents preferably (carbocyclic aryl or heterocylic aryl)-lower alkyl.

Carbocyclic aryl-lower alkyl preferably represents aryl-straight chain or -branched C_{1-4}-alkyl in which carbocyclic aryl has meaning as defined above, e.g. benzyl or phenyl-(ethyl, propyl or butyl), each unsubstituted or substituted on the phenyl ring as defined for carbocyclic aryl above, advantageously optionally substituted benzyl.

Heterocyclic aryl-lower alkyl represents preferably straight chain or branched heterocyclic aryl-C_{1-4}-alkyl in which heterocyclic aryl has meaning as defined above, e.g. 2-, 3- or 4-pyridylmethyl or (2, 3- or 4-pyridyl)-(ethyl, propyl or butyl); or 2- or 3-thienylmethyl or (2- or 3-thienyl)-(ethyl, propyl or butyl); 2-, 3- or 4-quinolinylmethyl or (2-, 3- or 4-quinolinyl)-(ethyl, propyl or butyl); or 2- or 4-thiazolylmethyl or (2- or 4-thiazolyl)-(ethyl, propyl or butyl).

Cycloalkyl-lower alkyl represents e.g. (cyclopentyl- or cyclohexyl)-(methyl or ethyl).

Biaryl-lower alkyl represents e.g. 4-biphenylyl-(methyl or ethyl).

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methyl-ammonium salts.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The compounds of the invention exhibit valuable pharmacological properties in mammals and are particularly useful as inhibitors of cathepsin K.

The cathepsin K inhibitory effects of the compound of the invention can be determined in vitro by measuring the inhibition of e.g. recombinant human cathepsin K.

The in vitro assay is carried out as follows:

For cathepsin K:

The assay is performed in 96 well microtiter plates at ambient temperature using recombinant human cathepsin K. Inhibition of cathepsin K is assayed at a constant enzyme (0.16 nM) and substrate concentration (54 mM Z-Phe-Arg-AMCA - Peptide Institute Inc.

Osaka, Japan) in 100 mM sodium phosphate buffer, pH 7.0, containing 2 mM dithiothreitol, 20 mM Tween 80 and 1 mM EDTA. Cathepsin K is preincubated with the inhibitors for 30 min, and the reaction is initiated by the addition of substrate. After 30 min incubation the reaction is stopped by the addition of E-64 (2 mM), and fluorescence intensity is read on a multi-well plate reader at excitation and emission wavelengths of 360 and 460 nm, respectively.

In view of their activity as inhibitors of cathepsin K, Compounds of the Invention are particularly useful in mammals as agents for treatment and prophylaxis of diseases and medical conditions involving elevated levels of cathepsin K. Such diseases include diseases involving infection by organisms such as pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei, crithidia fusiculata, as well as parasitic diseases such as schistosomiasis and malaria, tumours (tumour invasion and tumour metastasis), and other diseases such as metachromatic leukodystrophy, muscular dystrophy, amytrophy and similar diseases.

Cathepsin K, has been implicated in diseases of excessive bone loss, and thus the Compounds of the Invention may be used for treatment and prophylaxis of such diseases, including osteoporosis, gingival diseases such as gingivitis and periodontitis, Paget's disease, hypercalcemia of malignancy, e.g. tumour-induced hypercalcemia and metabolic bone disease. Also the Compounds of the Invention may be use for treatment or prophylaxis of diseases of excessive cartilage or matrix degradation, including osteoarthritis and rheumatoid arthritis as well as certain neoplastic diseases involving expression of high levels of proteolytic enzymes and matrix degradation.

Compounds of the Invention, are also indicated for preventing or treating coronary disease, atherosclerosis (including atherosclerotic plaque rupture and destabilization), autoimmune diseases, respiratory diseases and immunologically mediated diseases (including transplant rejection).

Compounds of the Invention are particularly indicated for preventing or treating osteoporosis of various genesis (e.g. juvenile, menopausal, post-menopausal, post-traumatic, caused by old age or by cortico-steroid therapy or inactivity).

Beneficial effects are evaluated in in vitro and in vivo pharmacological tests generally known in the art, and as illustrated herein.

The above cited properties are demonstrable in in vitro and in vivo tests, using advantageously mammals, e.g. rats, mice, dogs, rabbits, monkeys or isolated organs and tissues,

as well as mammalian enzyme preparations, either natural or prepared by e.g. recombinant technology. Compounds of the Invention can be applied in vitro in the form of solutions, e.g. preferably aqueous solutions or suspensions, and in vivo either enterally or parenterally, advantageously orally, e.g. as a suspension or in aqueous solution, or as a solid capsule formulation. The dosage in vitro may range between about 10^{-5} molar and 10^{-9} molar concentrations. The dosage in vivo may range, depending on the route of administration, between about 0.1 and 100 mg/kg.

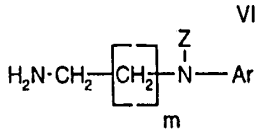
The antiarthritic efficacy of the compounds of the invention for the treatment of rheumatoid arthritis can be determined using models such as or similar to the rat model of adjuvant arthritis, as described previously (R.E. Esser, et. al. J. Rheumatology, 1993, 20, 1176.)

The efficacy of the compounds of the invention for the treatment of osteoarthritis can be determined using models such as or similar to the rabbit partial lateral meniscectomy model, as described previously (Colombo et al. Arth. Rheum. 1993 26, 875-886). The efficacy of the compounds in the model can be quantified using histological scoring methods, as described previously (O'Byrne et al. Inflamm Res 1995, 44, S117-S118).

The efficacy of the compounds of the invention for the treament of osteoporosis can be determined using an animal model such as the ovariectomised rat or other similar species, e.g. rabbit or monkey, in which test compounds are administered to the animal and the presence of markers of bone resorption are measured in urine or serum (e.g. as described in Osteoporos Int (1997) 7:539-543).

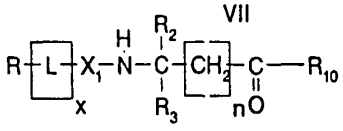
The compounds of the invention of formula I are prepared by:

a) reacting a compound of formula VI



VI

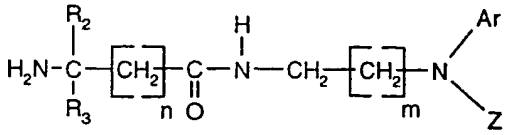
wherein Ar and m are as previously defined and Z is H, an amino protecting group or a solid phase support, with a compound of formula VII



VII

wherein R, R_2, R_3, L, X_1, x and n are as previously defined and R_{10} is OH or a leaving group; or

b) for preparation of a compound of formula I in which $-X_1-$ is -C(O)- and x is 0, reacting a compound of formula VIII



VIII

wherein R_2, R_3, Ar, n and m are as previously defined and Z is H, an amino protecting group or solid phase support, with a compound of formula $RCOR_{10}$, wherein R and R_{10} are as defined above;

and in the above processes, if required, temporarily protecting any interfering reactive groups and then isolating the resulting compound of the invention; and if desired, converting any resulting compound into another compound of the invention; and/or if desired, converting a resulting compound into a salt or ester, or a resulting salt or ester into the free acid or base or into another salt or ester; and if required recovering the resulting product from a solid phase.

Appropriate protecting groups are used for starting compounds and intermediates, for instance as hereinafter described in the Examples.

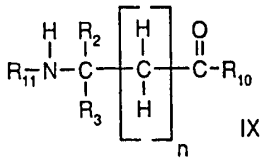
Linking of the amine of formula VI with the amino acid derivative of formula VII, according to process (a), can be carried out according to methods well known in the art for the formation of amide bonds, for instance as hereinafter described in the Examples. Thus for example, the amine of formula VI may be used in the form of an acid salt, e.g. the hydrochloride salt. When R_{10} is a suitable leaving group, the reaction may be carried out in an organic solvent, e.g. DMF, in the presence of a base, such as DIEA (diisopropylethylamine), for instance at room temperature. Suitable leaving groups as R_{10} are activated ester groups, such as hydroxy-succinimide or hydroxybenzotriazole: Typically when R_{10} is OH, a coupling reagent such as HATU is normally used.

The amine starting material of formula VI may be prepared by reacting the corresponding arylamine of formula $Ar-NH_2$, preferably in the form of an acid salt, e.g. $Ar-NH_2.HCl$, with oxazolidinone in the presence of a suitable solvent, such as 2-(2-methoxyethoxy)ethanol, preferably at elevated temperature, e.g. a temperature of ca. 170°C.

The arylaminoalkyl aminoacid amide derivative of formula VIII may be reacted with the compound of formula $R-COR_{10}$ to form an amide bond substantially as described above. Both

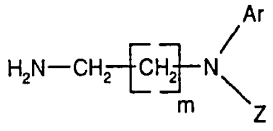
solution and solid phase synthesis procedures may be used. Thus for example, the derivative of formula VIII, attached to a solid phase, e.g. Rink resin, is contacted with the acid R-COOH in solution in an organic solvent, e.g. DMF, in the presence of a coupling reagent such as HATU and a base such DIEA. The resulting product may be cleaved from the solid phase; for instance, by acid treatment, e.g. TFA/CH_2Cl_2. Alternatively when R_{10} is a suitable leaving group, the derivative of formula VIII, and the compound of formula R-COR_{10} can be coupled in the presence of a base e.g. DIEA and in a solvent such as DMF.

The derivative of formula VIII may be prepared by linking a protected amino acid of formula IX



IX

wherein R_2, R_3 and R_{10} are as defined above, and R_{11} is an amino protecting, e.g. Fmoc, Cbz, or BOC, with an arylaminoalkylamine of formula X



X

wherein Ar and Z are as defined above. If desired the arylaminoalkylamine of formula X may be linked to a solid support, by linking an appropriately protected form of the arylaminoalkylamine of formula Ar-NH-$(CH_2)_m$-CH_2-NH_2 to an appropriate solid phase, e.g. Rink resin, using reagents and procedures analogous to those customarily used in solid phase chemistry; for instance, as hereinafter described in the Examples.

Compounds of the invention are either obtained in the free form, or as a salt thereof if salt forming groups are present, or as esters if ester forming groups are present.

Compounds of the Invention which have acidic groups may be converted into salts with pharmaceutically acceptable bases, e.g. an aqueous alkali metal hydroxide, advantageously in the presence of an ethereal or alcoholic solvent, such as a lower alkanol. Resulting salts may be converted into the free compounds e.g. by treatment with acids. These or other salts can also be used for purification of the compounds obtained. Ammonium salts are obtained by reaction with the appropriate amine, e.g. diethylamine, and the like.

Compounds of the Invention having basic groups can be converted into acid addition salts, especially pharmaceutically acceptable salts. These are formed, for example, with inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric or hydrohalic acid, or with organic carboxylic acids, such as (C_1-C_4)alkanecarboxylic acids which, for example, are unsubstituted or substituted by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, succinic, maleic or fumaric acid, such as hydroxycarboxylic acids, for example glycolic, lactic, malic, tartaric or citric acid, such as amino acids, for example aspartic or glutamic acid, or with organic sulfonic acids, such as (C_1-C_4)-alkylsulfonic acids (for example methanesulfonic acid) or arylsulfonic acids which are unsubstituted or substituted (for example by halogen). Preferred are salts formed with hydrochloric acid, methanesulfonic acid and maleic acid.

In view of the close relationship between the free compounds and the compounds in the form of their salts or esters, whenever a compound is referred to in this context, a corresponding salt or ester is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

The Compounds of the Invention which comprise free hydroxyl groups may also exist in the form of pharmaceutically acceptable, physiologically cleavable esters, and as such are included within the scope of the invention. Such pharmaceutically acceptable esters are preferably prodrug ester derivatives, such being convertible by solvolysis or cleavage under physiological conditions to the corresponding Compounds of the Invention which comprise free hydroxyl groups. Suitable pharmaceutically acceptable prodrug esters are those derived from a carboxylic acid, a carbonic acid monoester or a carbamic acid, advantageously esters derived from an optionally substituted lower alkanoic acid or an arylcarboxylic acid.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal, topical, and parenteral administration to mammals, including man, to inhibit cathepsin K activity, and for the treatment of cathepsin K dependent disorders, in particular inflammation, osteoporosis, rheumatoid arthritis and osteoarthritis, and comprise an effective amount of a pharmacologically active compound of the invention, alone or in combination, with one or more pharmaceutically acceptable carriers.

More particularly, the pharmaceutical compositions comprise an effective cathepsin K inhibiting amount of a Compound of the Invention.

The pharmacologically active Compounds of the Invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application.

Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75%, preferably about 1 to 50%, of the active ingredient.

Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable formulations for transdermal application include an effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. Matrix transdermal formulations may also be used.

Suitable formulations for topical application, e.g. to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

The pharmaceutical formulations contain an effective cathepsin K inhibiting amount of a Compound of the Invention as defined above, either alone or in combination with another therapeutic agent.

In conjunction with another active ingredient, a Compound of the Invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation. The dosage of active compound administered is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration. A unit dosage for oral administration to a mammal of about 50 to 70 kg may contain between about 5 and 500 mg of the active ingredient.

The present invention also relates to methods of using Compounds of the Invention and their pharmaceutically acceptable salts, or pharmaceutical compositions thereof, in mammals for inhibiting cathepsin K, and for the treatment of cathepsin K dependent conditions, such as the cathepsin K dependent conditions, described herein, e.g. inflammation, osteoporosis, rheumatoid arthritis and osteoarthritis.

Particularly the present invention relates to a method of selectively inhibiting cathepsin K activity in a mammal which comprises administering to a mammal in need thereof an effective cathepsin K inhibiting amount of a Compound of the Invention.

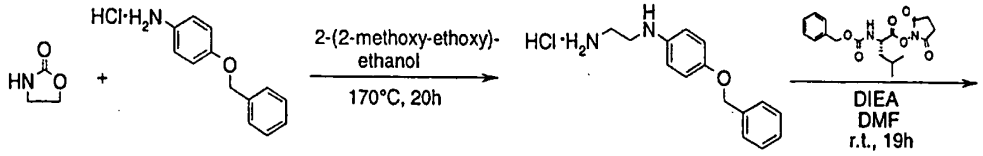
More specifically such relates to a method of treating osteoporosis, rheumatoid arthritis, osteoarthritis, and inflammation (and other diseases as identified above) in mammals comprises administering to a mammal in need thereof a correspondingly effective amount of a Compound of the Invention.

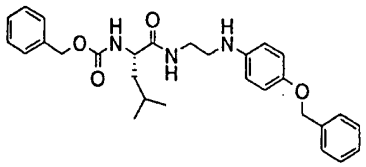
The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Centrigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g. microanalysis and spectroscopic characteristics (e.g. MS, IR, NMR). Abbreviations used are those conventional in the art.

EXAMPLES

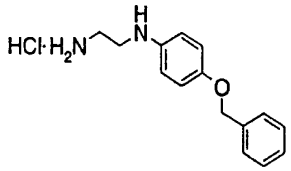
The following Examples 1 to 21 describe the synthesis of selected Compounds of the Invention using solution chemistry. The reaction scheme for synthesis of a typical arylaminoethyl amide, (S)-{1-[2-(4-Benzyloxy-phenylamino)-ethylcarbamoyl]-3-methyl-butyl}-carbamic acid benzyl ester is given below.

Example 1: Synthesis of (S)-{1-[2-(4-Benzyloxy-phenylamino)-ethylcarbamoyl]-3-methyl-butyl}-carbamic acid benzyl ester





A. Synthesis of *N1*-(4-Benzyloxy-phenyl)-ethyl-1,2-diamine hydrochloride

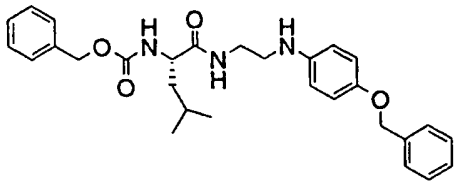


A suspension of 4-benzyloxy aniline hydrochloride (70.8 g, 0.3 mol) and 2-oxazolidinone in 2-(2-methoxyethoxy)ethanol (110 mL) is heated while being stirred at 170°C in an oil bath. After 20 h the heating bath is removed and the dark reaction mixture is allowed to cool to r.t.. The diamine hydrochloride crystallizes on standing, and is collected by filtration and washed with ether.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.06 (m, br, 3H), 7.38 (m, 5H), 6.84 (d, 2H), 6.57 (d, 2H), 4.98 (s, 2H), 3.2 (m, 2H), 2.94 (m, 2H).

MS (ES+): 243 $(M+H)^+$.

B. Synthesis of (S)-{1-[2-(4-Benzyloxy-phenylamino)-ethylcarbamoyl]-3-methyl-butyl}-carbamic acid benzyl ester

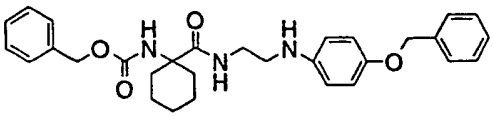


To a suspension of 4-Benzyloxy-phenyl)-ethyl-1,2-diamine hydrochloride (0.438 g, 1.10 mmol) in DMF (3 mL) is added DIEA (0.52 mL, 3.0 mmol) and Z-leucine N-hydroxy-succinimidate (0.362 g, 1 mmol). The resultant suspension is stirred at r.t. for 16 h. After diluting the mixture with AcOEt, H_2O is added and the layers are separated. The organic phase is washed with H_2O and brine, dried (Na_2SO_4) and the solvent is removed *in vacuo*. The residue is recrystallized from ether /hexane.

mp: 137- 139°C.

MS (ES+): 490 $(M+H)^+$.

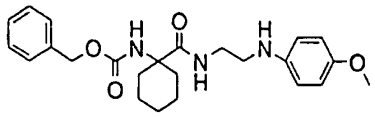
In formulae given below and elsewhere in the present description, e.g. for the compounds of Examples 2-137, carbon-carbon bonds are depicted by single lines for carbon-carbon single bonds and double lines for carbon-carbon double bonds; carbon atoms are not shown nor are hydrogen substituents on carbon atoms; whereas oxygen atoms are depitced by O and Nitrogen atoms by N, and hydrogen substituents on nitrogen atoms are depicted by H. Thus  depicts an n-propyl substituent, i.e. - CH_2-CH_2-CH_3, and depicts a methyl substituent, i.e. -CH_3.

Example Number	Compound
2	

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.48- 7.30 (m, 10H), 6.84 (d, 2H), 6.68 (m, br, 1H), 6.58 (d, 2H), 5.09 (s, 2H), 5.00 (s, 2H), 4.97 (s, 1H), 3.46 (m, 2H), 3.21 (m, 2H), 2.08- 1.26 (m, 10H).

MS (ES+): 501 $(M+H)^+$.

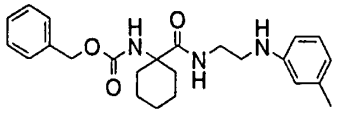
3



mp: 123- 124°C.

MS (ES+): 426 $(M+H)^+$.

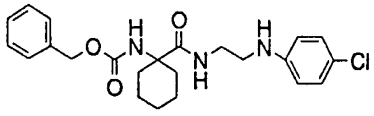
4



mp: 121- 122°C.

MS (ES+): 410 $(M+H)^+$.

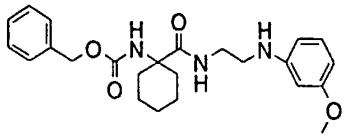
5



mp: 144- 145°C.

MS (ES+): 430 $(M+H)^+$.

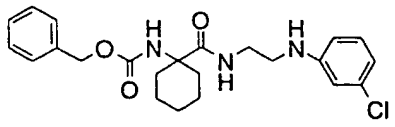
6



mp: 80- 82°C.

MS (ES+): 426 $(M+H)^+$.

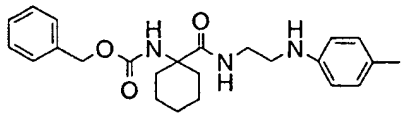
7



mp: 120- 121°C.

MS (ES+): 430 $(M+H)^+$.

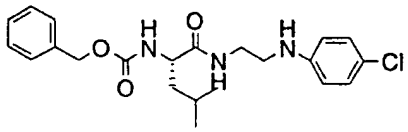
8



mp: 147- 148°C.

MS (ES+): 410 $(M+H)^+$.

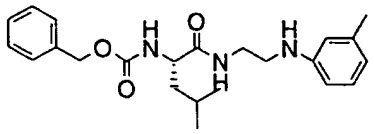
9



mp: 129- 130°C.

MS (ES+): 418 $(M+H)^+$.

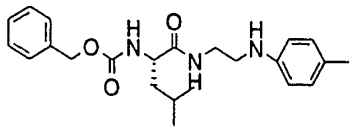
10



mp: 106- 108°C.

MS (ES+): 398 $(M+H)^+$.

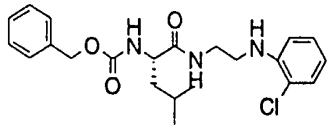
11



mp: 105- 106°C.

MS (ES+): 398 $(M+H)^+$.

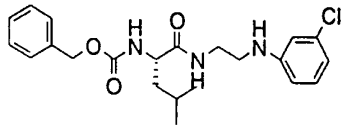
12



mp: 125- 126°C.

MS (ES+): 418 $(M+H)^+$.

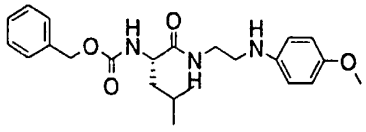
13



mp: 105- 107°C.

MS (ES+): 418 $(M+H)^+$.

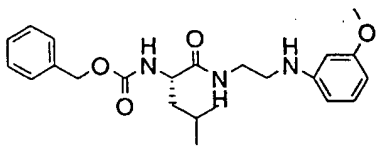
14



mp: 103- 105°C.

MS (ES+): 414$(M+H)^+$.

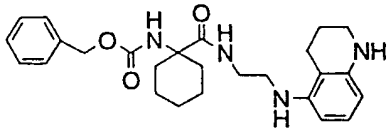
15



mp: 95- 97°C.

MS (ES+): 414$(M+H)^+$.

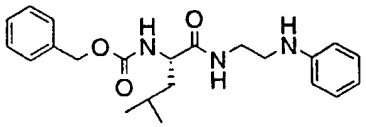
16



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34 (s, 5H), 7.20 (m, 1H), 6.90 (t, 1H), 6.80 (m, br, 1H), 6.00 (t, 2H), 5.08 (s, 2H), 3.50 (m, 2H), 3.24 (m, 2H), 3.19 (m, 2H), 2.40 (m, 2H), 2.08- 1.1 (m, 12H).

MS (ES+): 451$(M+H)^+$.

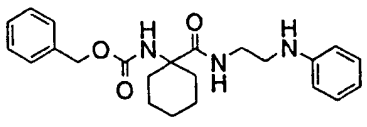
17



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.32 (s, 5H), 7.27- 7.12 (m, 3H), 6.80 (d, 1H), 6.70 (d, 1H), 6.54 (m, br, 1H), 5.19 (d, 1H), 5.08 (s, 2H), 4.12 (m, 1H), 3.49 (m, 2H), 3.28 (m, 2H), 1.71- 1.42 (m, 3H), 0.9 (d, 6H).

MS (ES+): 384$(M+H)^+$.

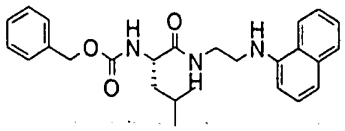
18



mp: 129- 131°C.

MS (ES+): 396$(M+H)^+$.

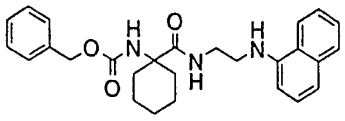
19



mp: 125- 128°C.

MS (ES+): 434$(M+H)^+$.

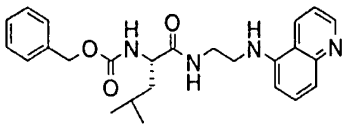
20



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.92 (m, 1H), 7.78 (m, 1H), 7.48- 7.12 (m, 10H), 6.87 (m, br, 1H), 6.54 (d, 1H), 5.16 (m, br, 1H), 4.98 (s, 2H), 3.60 (m, 2H), 3.40 (m, 2H), 2.00- 1.22 (m, 10H).

MS (ES+): 446$(M+H)^+$.

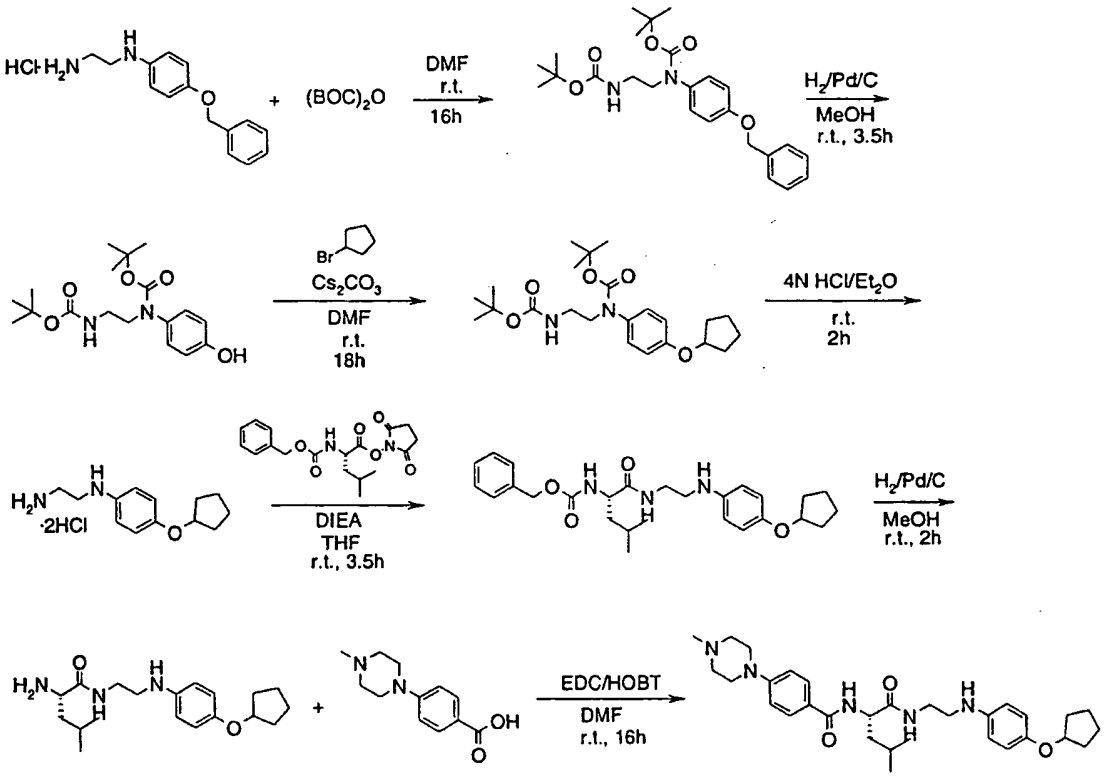
21



mp: 64 – 68°C

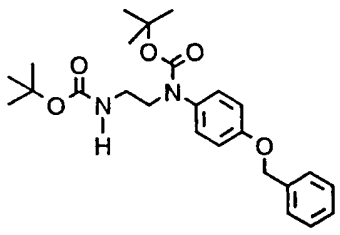
MS (ES+): 435 $(M+H)^+$.

The synthesis of further selected Compounds of the Invention using solution chemistry is described in the following Examples 22-106. The reaction scheme for a typical Compound of the Invention, (S)-*N*-{1-[2-(4-Cyclopentyloxy-phenylamino)-ethylcarbamoyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide. is given below.



Example 22: Synthesis of (S)-*N*-{1-[2-(4-Cyclopentyloxy-phenylamino)-ethylcarbamoyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide

A. Synthesis of (4-Benzyloxy-phenyl)-(2-*tert*-butoxycarbonylamino-ethyl)-carbamic acid *tert*-butyl ester

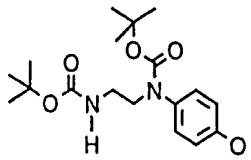


To a suspension of *N1*-(4-benzyloxy-phenyl)-ethyl-1,2-diamine hydrochloride (21.9 g, 50.28 mmol) in DMF (150 mL) is added $(BOC)_2O$ (24.0 g, 110 mmol) and DIEA (18.8 mL, 110 mmol). The mixture is stirred for 16 h at r.t.. After diluting the mixture with AcOEt, H_2O is added and the layers are separated. The organic phase is washed with H_2O and brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue is purified by flash chromatography (1:5 AcOEt:hexane) to provide (4-Benzyloxy-phenyl)-(2-*tert*-butoxycarbonylamino-ethyl)-carbamic acid *tert*-butyl ester as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.40 (m, 5H), 7.1 (d, 2H), 6.93 (d, 2H), 5.08 (s, 2H), 4.92 (m, br, 1H), 3.70 (m, 2H), 3.29 (m, 2H), 1.93 (s, 18H).

MS (ES+): 443 $(M+H)^+$.

B. Synthesis of (2-*tert*-Butoxycarbonylamino-ethyl)-(4-hydroxy-phenyl)-carbamic acid *tert*-butyl ester

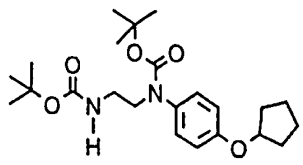


A solution of (4-Benzyloxy-phenyl)-(2-*tert*-butoxycarbonylamino-ethyl)-carbamic acid *tert*-butyl ester (17 g, 38.4 mmol) in MeOH (170 mL) is hydrogenated over Pd/C(10%) (2.5 g) at r.t. for 3.5 h. Pd/C is removed by filtration and the solvent evaporated *in vacuo*.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.70 (d, 2H), 6.53 (d, 2H), 4.85 (m, br, 1H), 3.32 (m, 2H), 3.21 (m, 2H), 1.44 (s, 18H).

MS (ES+): 353 $(M+H)^+$.

C. Synthesis of (2-*tert*-Butoxycarbonylamino-ethyl)-(4-cyclopentyloxy-phenyl)-carbamic acid *tert*-butyl ester

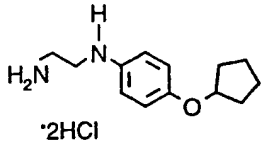


To a solution of (2-*tert*-Butoxycarbonylamino-ethyl)-(4-hydroxy-phenyl)-carbamic acid *tert*-butyl ester (10.57 g, 30 mmol) in DMF (60 mL) is added bromocyclopentane (9.65 mL, 90 mmol).The

resulting suspension is stirred at r.t. for 18 h. After diluting the mixture with AcOEt, H_2O is added and the layers are separated. The organic phase is washed with H_2O and brine, dried (Na_2SO_4) and the solvent removed *in vacuo*.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.04 (d, 2H), 6.80 (d, 2H), 4.92 (m, br, 1H), 4.71 (m, 1H), 3.69 (m, 2H), 3.24 (m, 2H), 1.98- 1.42 (m, 8H), 1.40 (s. 18H).
MS (ES+): 421 $(M+H)^+$.

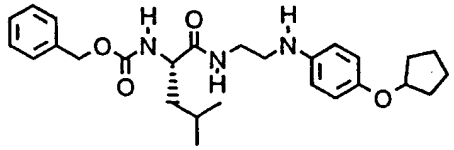
D. Synthesis of *N*1-(4-Cyclopentyloxy-phenyl)-ethylen-1,2-diamine dihydrochloride



To a solution of (2-*tert*-Butoxycarbonylamino-ethyl)-(4-cyclopentyloxy-phenyl)-carbamic acid *tert*-butyl ester in THF (40 mL) is added 4N HCl/ether (100 mL).The mixture is stirred for 2 h at r.t. during this time the product precipitated. The product is collected by filtration and dried *in vacuo*.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.45 (s, br, 3H), 7.41 (d, 2H), 7.00 (d, 2H), 4.81 (m, 1H), 3.49 (m, 2H), 3.20 (m, 2H), 1.99- 1.52 (m, 8H).
MS (ES+): 221 $(M+H)^+$.

E. Synthesis of (S){1-[2-(4-Cyclopentyloxy-phenylamino)-ethylcarbamoyl]-3-methyl-butyl}-carbamic acid benzyl ester

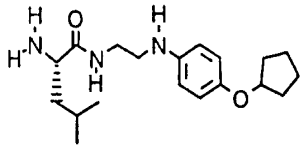


To a suspension of *N1*-(4-Cyclopentyloxy-phenyl)-ethylen-1,2-diamine dihydrochloride (0.260 g, 0.88 mmol) in DMF (2 mL) is added DIEA (0.38 mL, 2.22 mmol) and Z-leucine N-hydroxy-succinimidate (0.321 g, 0.88 mmol). The resultant suspension is stirred at r.t. for 3.5 h. After diluting the mixture with AcOEt, H_2O is added and the layers are separated. The organic phase is washed with H_2O and brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue is

purified by flash chromatography (1:3 AcOEt:hexane) to provide (S)-{1-[2-(4-Cyclopentyloxy-phenylamino)-ethylcarbamoyl]-3-methyl-butyl}-carbamic acid benzyl ester as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.32 (s, 5H), 6.74 (d, 2H), 6.55 (d, 2H), 6.39 (m, br, 1H), 5.19 (m, 1H), 5.1 (d, 2H), 4.62 (m, 1H), 4.13 (m,1H), 3.45 (m, 2H), 3.21 (m, 2H), 1.82 - 1.5 (m, 11H), 0.9 (d, 6H).
MS (ES+): 468 $(M+H)^+$.

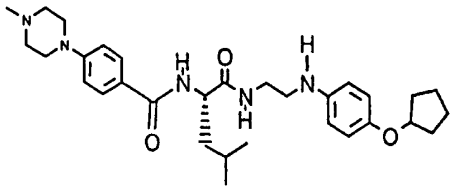
F. Synthesis of (S)-2-Amino-4-methyl-pentanoic acid [2-(4-cyclopentyloxy-phenylamino)-ethyl]-amide



A solution of (S)-{1-[2-(4-Cyclopentyloxy-phenylamino)-ethylcarbamoyl]-3-methyl-butyl}-carbamic acid benzyl ester (0.333 g, 0.712 mmol) in MeOH (7 mL) is hydrogenated over Pd/C(10%) (0.07 g) at r.t. for 2 h. Pd/C is removed by filtration and the solvent evaporated *in vacuo*.

^{1}H-NMR (300 MHz,$CDCl_3$) δ: 7.57 (m, br, 1H), 6.78 (d, 2H), 6.58 (d, 2H), 4.63 (m, 1H), 3.71 (m, 1H), 3.50 (m, 2H), 3.24 (m, 2H), 1.90- 1.52 (m, 10H), 1.49- 1.21 (m, 3H), 0.95 (d, 6H).
MS (ES+): 334$(M+H)^+$.

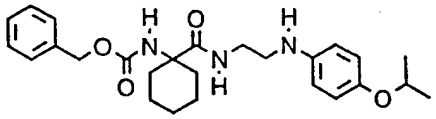
G. Synthesis of (S)-*N*-{1-[2-(4-Cyclopentyloxy-phenylamino)-ethylcarbamoyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide



To a suspension of 4-(4-Methyl-piperazin-1-yl)-benzoic acid hydrochloride (0.085 g, 0.33 mmol) in DMF (0.5 mL) is added EDC (0.063 g, 0.33 mmol), HOBT (0.052 g, 0.33 mmol) and DIEA (0.08 mL, 0.49 mmol). The mixture is stirred at r.t. for 10 min and then (S)-2-Amino-4-

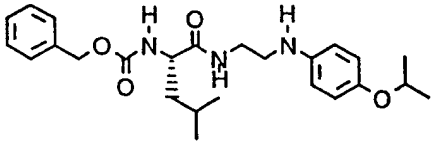
methyl-pentanoic acid [2-(4-cyclopentyloxy-phenylamino)-ethyl]-amide (0.11 g, 0.33 mmol) dissolved in DMF (1 mL) is added. The mixture is stirred at r.t. for 16 h. After diluting the mixture with AcOEt, H_2O is added and the layers were separated. The organic phase is washed with H_2O and brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue is crystallized from AcOEt/Et_2O to provide (S)-*N*-{1-[2-(4-Cyclopentyloxy-phenylamino)-ethylcarbamoyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.68 (d, 2H), 6.88 (d, 2H), 6.78 (m, br, 1H), 6.74 (d, 2H), 6.55 (d, 2H), 6.47 (d, 1H), 4.62 (m, 1H), 3.45 (m, 2H), 3.30 (m, 4H), 3.21 (m, 2H), 2.57 (m, 4H), 2.35 (s, 3H), 1.86- 1.52 (m, 10H), 1.28 (m, 1H), 0.96 (d, 6H).
MS (ES+): 536 $(M+H)^+$.

Example Number	Compound
23	

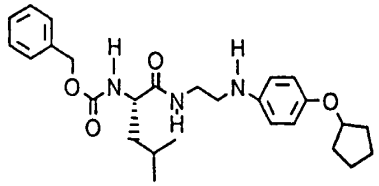
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.32 (s, 5H), 6.74 (d, 2H), 6.65 (m, br, 1H), 6.55 (d, 2H), 5.08 (s, 2H), 4.92 (s, 1H), 4.30 (m. 1H), 3.42 (m, 2H), 3.19 (m, 2H),1.98- 1.21 (m, 10H), 1.23 (d, 6H).
MS (ES+): 454 $(M+H)^+$.

24



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.32 (s, 5H), 6.74 (d, 2H), 6.55 (d, 2H), 6.30 (m, br, 1H), 5.12 (m, br, 1H), 5.10 (s, 2H), 4.32 (m, 1H), 4.11 (m, 1H), 3.45 (m, 2H), 3.20 (m, 2H), 1.62 (m, 3H), 1.25 (d, 6H), 0.90 (d, 6H).
MS (ES+): 442 $(M+H)^+$.

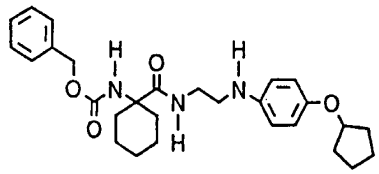
25



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.32 (s, 5H), 6.74 (d, 2H), 6.55 (d, 2H), 6.39 (m, br, 1H), 5.19 (m, 1H), 5.1 (d, 2H), 4.62 (m, 1H), 4.13 (m, 1H), 3.45 (m, 2H), 3.21 (m, 2H), 1.82 - 1.5 (m, 11H), 0.9 (d, 6H).

MS (ES+): 468 $(M+H)^+$.

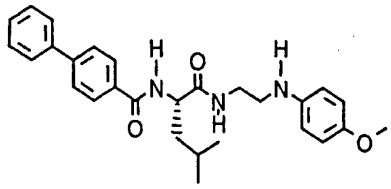
26



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35 (s, 5H), 6.76 (d, 2H), 6.68 (m, 1H), 6.55 (d, 2H), 5.08 (s,2H), 4.95 (s, 1H), 4.62 (s,1H), 3.45 (m, 2H), 3.20 (m, 2H), 2.02 - 1.3 (m, 18H).

MS (ES+): 480 $(M+H)^+$.

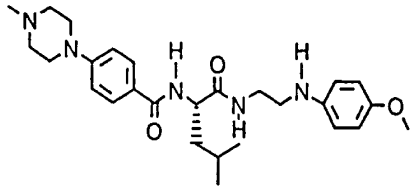
27



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.85 (d, 2H), 7.68- 7.40 (m, 7H), 6.77 (d, 2H), 6.61 (m, br, 1H), 6.60 (d, 2H), 4.61 (m, 1H), 3.73 (s, 3H), 3.49 (m, 2H), 3.28 (m, 2H), 1.73 (m, 3H), 0.99 (d, 6H).

MS (ES): 460 $(M+H)^+$.

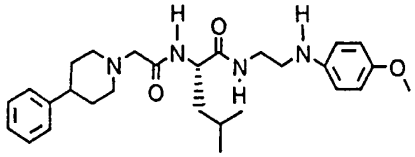
28



mp: 190 – 191°C.

MS (ES+): 482 $(M+H)^+$.

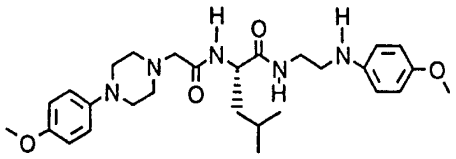
29



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.55 (d, 1H), 7.38 (m, 5H), 6.78 (d, 2H), 6.60 (d, 2H), 4.49 (m, 1H), 3.75 (s, 3H), 3.48 (m, 2H), 3.22 (m, 2H), 3.01 (s, 2H), 2.80 (m, 2H), 2.58- 2.21 (m, 3H), 1.90- 1.58 (m, 7H), 0.95 (d, 6H).

MS (ES+): 481 $(M+H)^+$.

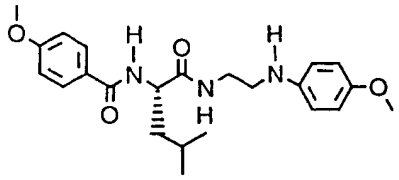
30



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.46 (d, 1H), 6.85 (s, 4H), 6.78 (d, 2H), 6.60 (d, 2H), 6.55 (m, br, 1H), 4.38 (m, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.50 (m, 2H), 3.22 (m, 2H), 3.12- 2.99 (m, 4H), 3.05 (s, 2H), 2.76 (m, 4H), 1.75- 1.55 (m, 3H), 0.94 (d, 6H).

MS (ES+): 512 $(M+H)^+$.

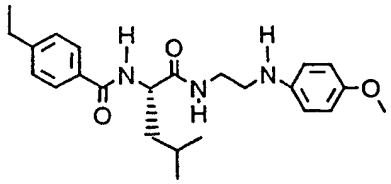
31



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.71 (d, 2H), 6.89 (d, 2H), 6.72 (d, 2H), 6.70 (m, br, 1H), 6.55 (d, 2H), 6.54 (m, br, 1H), 4.60 (m, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.42 (m, 2H), 3.22 (m, 2H), 1.70 (m, 3H), 0.94 (d, 6H).

MS (ES+): 414 $(M+H)^+$.

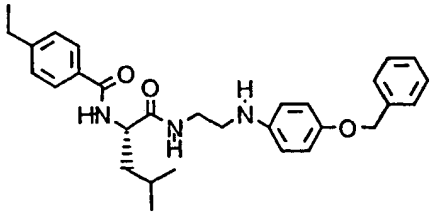
32



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.70 (d, 2H), 7.25 (d, 2H), 6.75 (d, 2H), 6.72 (m, br, 1H), 6.60 (m, br, 1H), 6.58 (d, 2H), 4.62 (m, 1H), 3.72 (s, 3H), 3.47 (m, 2H), 3.22 (m, 2H), 2.69 (q, 2H), 1.80- 1.62 (m, 3H), 1.24 (t, 3H), 0.96 (d, 6H).

MS (ES+): 412 $(M+H)^+$.

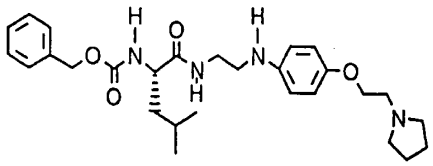
33



mp: 152 -154°C.

MS (ES+): 488 $(M+H)^+$.

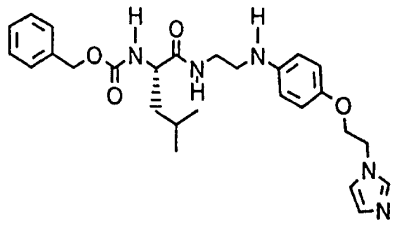
34



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34 (s, 5H), 6.80 (d, 2H), 6.58 (d, 2H), 6.32 (s, 1H), 5.12 (m, 1H), 5.10 (s, 2H), 4.11 (m, 1H), 4.02 (t, 2H), 3.46 (m, 2H), 3.21 (m, 2H), 2.86 (t, 2H), 2.60 (m, 4H), 1.80 (m,4H), 1.65 (m, 2H), 1.50 (m, 1H), 0.92 (d, 6H).

MS (ES+): 497 $(M+H)^+$.

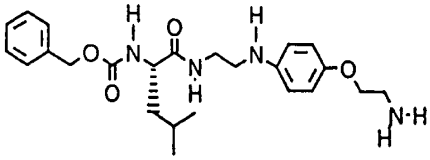
35



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.60 (m, 1H), 7.32 (s, 5H), 7.08 (m, 2H), 6.72 (d, 2H), 6.52 (d, 2H), 6.34 (m, br, 1H), 5.12 (m, br, 1H), 5.08 (s, 2H), 4.26 (m, 2H), 4.11 (m, 2H), 4.09 (m, 1H), 3.46 (m, 2H), 3.20 (m, 2H), 1.81- 1.60 (m, 3H), 0.88 (d, 6H).

MS (ES+): 494 $(M+H)^+$.

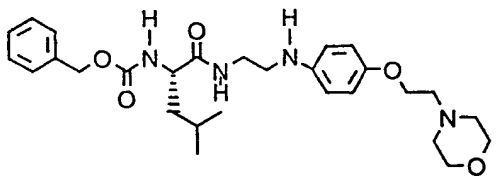
36



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.32 (s, 5H), 6.80 (d, 2H), 6.58 (d, 2H), 6.37 (m, br, 1H), 5.18 (m, br, 1H), 5.10 (s, 2H), 4.12 (m, 1H), 4.00 (t, 2H), 3.47 (m, 2H), 3.20 (m, 2H), 2.73 (t, 2H), 2.34 (s, 6H), 1.65 (m, 2H), 1.50 (m, 1H), 0.92 (d, 6H).

MS (ES+): 471$(M+H)^+$.

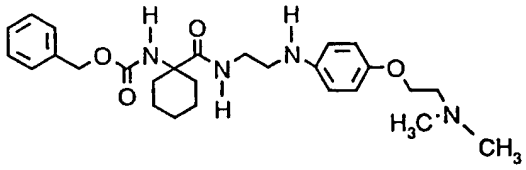
37



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34 (s, 5H), 6.79 (d, 2H), 6.56 (d, 2H), 6.32 (m, br, 1H), 5.12 (m, br, 1H), 5.09 (s, 2H), 4.12 (m, 1H), 4.02 (t, 2H), 3.73 (m, 4H), 3.45 (m, 2H), 3.21 (m, 2H), 2.75 (t, 2H), 2.56 (m, 4H), 1.77 (m, 2H), 1.50 (m, 1H), 0.90 (d, 6H).

MS (ES+): 513 $(M+H)^+$.

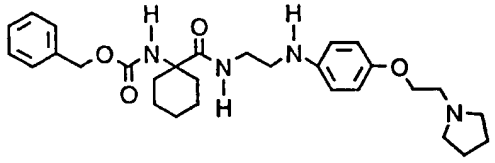
38



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34 (s, 5H), 6.78 (d, 2H), 6.67 (m, br, 1H), 6.56 (d, 2H), 5.08 (s, 2H), 4.95 (m, br, 1H), 4.01 (t, 2H), 3.45 (m, 2H), 3.19 (m, 2H), 2.80 (t, 2H), 2.40 (s, 6H), 2.05- 1.24 (m, 10H).

MS (ES+): 483 $(M+H)^+$.

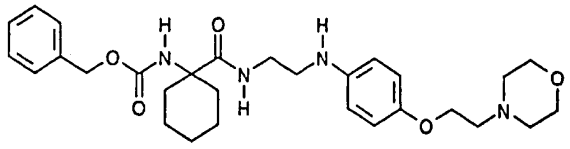
39



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.32 (s, 5H), 6.78 (d, 2H), 6.65 (m, br, 1H), 6.55 (d, 2H), 5.07 (s, 2H), 4.96 (m, br, 1H), 4.50 (t, 2H), 3.45 (m, 2H), 3.20 (m, 2H), 2.91 (t, 2H), 2.69 (m, 4H), 2.04- 1.24 (m, 14H).

MS (ES+): 509 $(M+H)^+$.

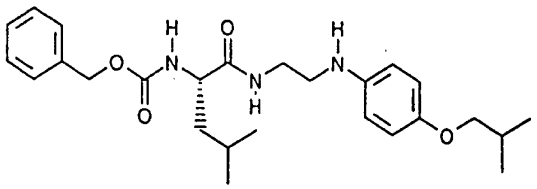
40



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34 (s, 5H), 6.78 (d, 2H), 6.62 (m, br, 1H), 6.50 (d, 2H), 5.08 (s, 2H), 4.96 (s, 1H), 4.02 (t, 2H), 3.73 (m, 4H), 3.44 (m, 2H), 3.20 (m, 2H), 2.74 (t, 2H), 2.54 (m, 4H), 2.06- 1.27 (m, 10H).

MS (ES+): 525 $(M+H)^+$.

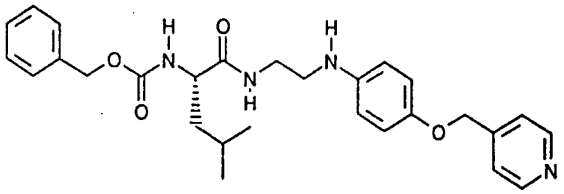
41



mp: 90 – 92°C.

MS (ES+): 456 $(M+H)^+$.

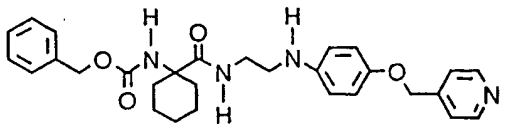
42



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.6 (d, 2H), 7.33 (m, 7H), 6.80 (d, 2H), 6.57 (d, 2H), 6.40 (m, br, 1H), 5.09 (m, br, 1H), 5.00 (s, 2H), 4.12 (m, 1H), 3.43 (m, 2H), 3.21 (m, 2H), 1.66 (m, 2H), 1.51 (m, 1H), 0.92 (d, 6H).

MS (ES+): 491$(M+H)^+$.

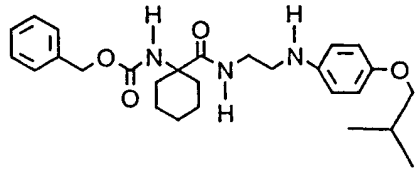
43



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.6 (d, 2H), 7.32 (m, 7H), 6.80 (d, 2H), 6.67 (m, br, 1H), 6.58 (d, 2H), 5.08 (s, 2H), 4.99 (s, 2H), 4.98 (s, 1H), 3.48 (m, 2H), 3.20 (m, 2H), 2.05- 1.28 (m, 10H).

MS (ES+): 503 $(M+H)^+$.

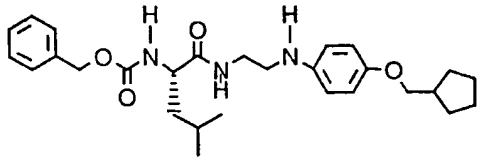
44



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35 (s, 5H), 6.76 (d, 2H), 6.66 (m, br, 1H), 6.58 (d, 2H), 5.08 (s, 2H), 4.98 (s, 1H), 3.64 (d, 2H), 3.47 (m, 2H), 3.20 (m, 2H), 2.08- 1.28 (m, 11H), 1.0 (d, 6H).

MS (ES+): 468 $(M+H)^+$.

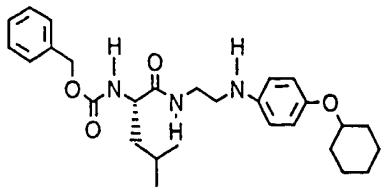
45



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35 (s, 5H), 6.29 (d, 2H), 6.57 (d, 2H), 6.36 (m, br, 1H), 5.12 (m, br, 1H), 5.09 (s, 2H), 4.12 (m, 1H), 3.74 (d, 2H), 3.46 (m, 2H), 3.20 (m, 2H), 2.30 (m, 1H), 1.90- 1.28 (m, 11H), 0.94 (d, 6H).

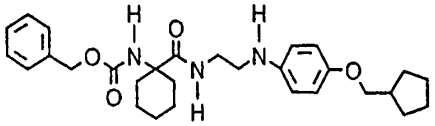
MS (ES+): 482 $(M+H)^+$.

46



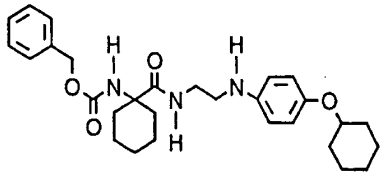
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35 (s, 5H), 6.80 (d, 2H), 6.55 (d, 2H), 6.33 (m, br, 1H), 5.10(s, 2H), 4.13 (m, 1H), 4.06 (m, 1H), 3.48 (m, 2H), 3.22 (m, 2H), 2.01-1.27 (m, 13H), 0.92 (d, 6H).
MS (ES+): 482 $(M+H)^+$.

47



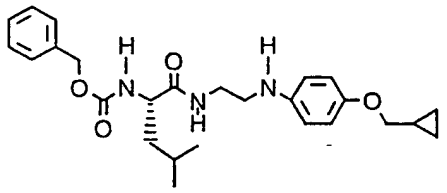
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35 (s, 5H), 6.78 (d, 2H), 6.68 (m, br, 1H), 6.58 (d, 2H), 5.09 (s, 2H), 4.96 (s, 1H), 3.75 (d, 2H), 3.46 (m, 2H), 3.21 (m, 2H),2.31 (m, 1H) 2.08- 1.24 (m, 18H).
MS (ES+): 494 $(M+H)^+$.

48



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35 (s, 5H), 6.78 (d, 2H), 6.67 (m, br, 1H), 6.58 (d, 2H), 5.10 (s, 2H), 4.97 (s, 1H), 4.02 (s, 1H), 3.45 (m, 2H), 3.20 (m, 2H), 2.02- 1.24 (m, 20H).
MS (ES+): 494 $(M+H)^+$.

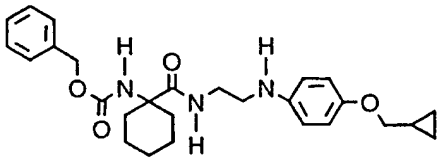
49



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34 (s, 5H), 6.79 (d, 2H), 6.58 (d, 2H), 6.40 (m, br, 1H), 5.19 (m, br, 1H), 5.10 (s, 2H), 4.12 (m, 1H), 3.71 (d, 2H), 3.45 (m, 2H), 3.20 (m, 2H),1.65 (m, 2H), 1.50 (m, 1H), 0.91 (d, 6H), 0.62 (m, 2H), 0.30 (m, 2H).

MS (ES+): 454 $(M+H)^+$.

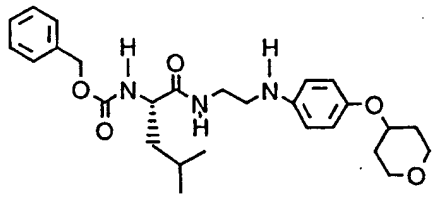
50



mp: 140 –145°C.

MS (ES+): 466 $(M+H)^+$.

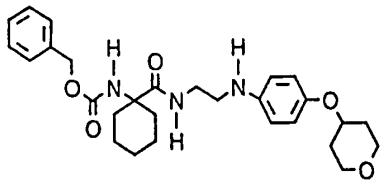
51



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34 (s, 5H), 6.80 (d, 2H), 6.58 (d, 2H), 6.36 (m, br, 1H), 5.13 (m, br, 1H), 5.10 (s, 2H), 4.29 (m, 1H), 4.13 (m, 1H), 3.97 (m, 2H), 3.52 (m, 2H), 3.48 (m, 2H), 3.21 (m, 2H), 1.97 (m, 2H), 1.75 (m, 2H), 1.64 (m, 2H), 1.51(m, 1H), 0.92 (d, 6H).

MS (ES+): 484 $(M+H)^+$.

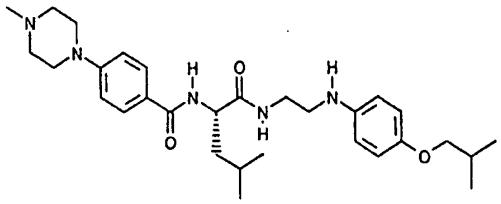
52



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34 (s, 5H), 6.79 (d, 2H), 6.68 (m, br, 1H), 6.57 (d, 2H), 5.06 (s, 2H), 4.95 (s, 1H), 4.28 (m, 1H), 3.97 (m, 2H), 3.52 (m, 2H), 3.47 (m, 2H), 3.22 (m, 2H), 2.20- 1.26 (m, 14H).

MS (ES+): 496 $(M+H)^+$.

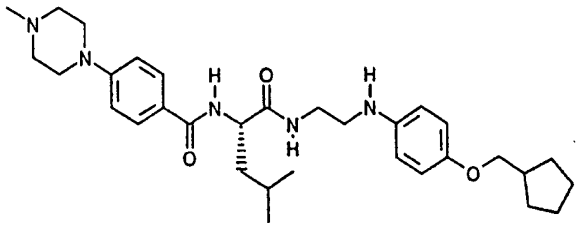
53



mp: 191 –193°C

MS (ES+): 524 $(M+H)^+$.

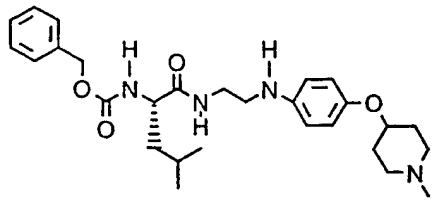
54



^{1}H-NMR (300 MHz, CD_3OD) δ: 7.78 (d, 2H), 6.95 (d, 2H), 6.71 (d, 2H), 6.60 (d, 2H), 4.54 (m, 1H), 3.72 (d, 2H), 3.35 (m, 11H), 3.18 (t, 2H), 2.62 (m, 2H), 2.25 (m, 1H), 1.89- 1.57 (m, 8H), 1.36 (m, 2H), 1.22 (m, 1H), 0.94 (d, 6H).

MS (ES+): 550 $(M+H)^+$.

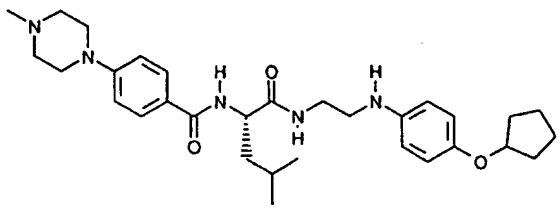
55



^{1}H-NMR (400 MHz, DMSO-d_6, 120°C): 7.69 (t, 1H), 7.34 (s, 5H), 6.92 (m, br, 1H), 6.72 (d, 2H), 6.51 (d, 2H), 5.05 (s, 2H), 4.90 (m, br, 1H), 4.10 (m, 1H), 4.01 (m, 1H), 3.35 (m, 2H), 3.05 (m, 2H), 2.76 (m, 2H), 2.38 (m, 2H), 2.30 (s, 3H), 1.90 (m, 2H), 1.71- 1.61 (m, 3H), 1.50 (t, 2H), 0.88 (dd, 6H).

MS (ES+): 497 $(M+H)^+$.

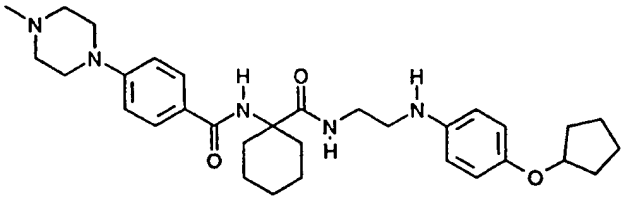
56



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.68 (d, 2H), 6.88 (d, 2H), 6.78 (m, br, 1H), 6.74 (d, 2H), 6.55 (d, 2H), 6.47 (d, 1H), 4.62 (m, 1H), 3.45 (m, 2H), 3.30 (m, 4H), 3.21 (m, 2H), 2.57 (m, 4H), 2.35 (s, 3H), 1.86- 1.52 (m, 10H), 1.28 (m, 1H), 0.96 (d, 6H).

MS (ES+): 536 $(M+H)^+$.

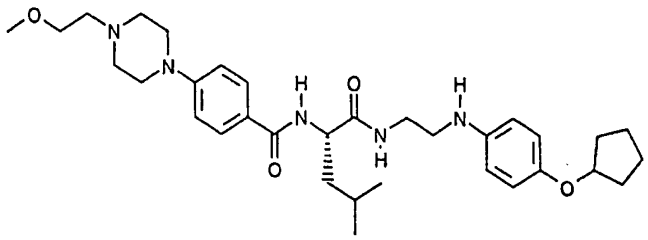
57



^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.76 (d, 2H), 7.58 (s, 1H), 7.49 (t, 1H), 6.94 (d, 2H), 6.66 (d, 2H), 6.49 (d, 2H), 4.40 (m, 1H), 4.60 (m, 1H), 3.22 (m, 4H), 3.20 (m, 2H), 2.97 (m, 2H), 2.44 (m, 4H), 2.23 (s, 3H), 2.12 (m, 2H), 1.89- 1.18 (m, 16H).

MS (ES+): 548 $(M+H)^+$.

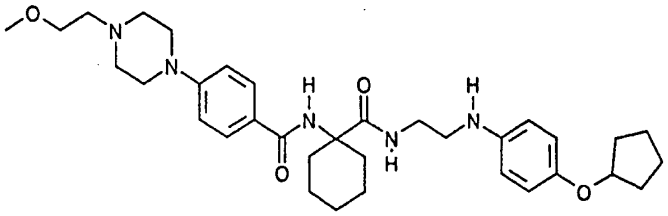
58



^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.08 (d, 1H),7.97 (m, 1H), 7.79 (d, 2H), 6.94 (d, 2H), 6.67 (d, 2H), 6.49 (d, 2H), 5.08 (t, 1H), 4.60 (m, 1H), 4.45 (m, 1H), 3.48 (t, 2H), 3.26 (s, 3H), 3.25 (m, 6H), 3.00 (m, 2H), 2.54 (m, 6H), 1.86- 1.49 (m, 11H), 0.88 (d, 6H).

MS (ES+): 580 $(M+H)^+$.

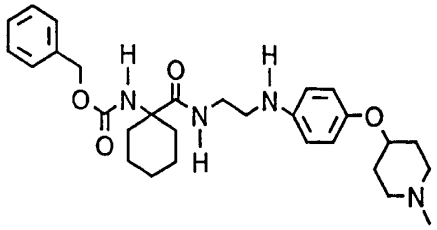
59



^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.76 (d, 2H), 7.58 (s, 1H), 7.50 (t, 1H), 6.94 (d, 2H), 6.64 (d, 2H), 6.48 (d, 2H), 4.91 (t, 1H), 4.60 (m, 1H), 3.49 (t, 2H), 3.25 (s, 3H), 3.25- 3.17 (m, 6H), 2.97 (m, 2H), 2.55 (m, 6H), 2.28- 1.21 (m, 18H).

MS (ES+): 592 $(M+H)^+$.

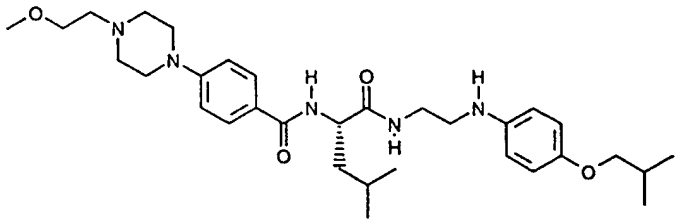
60



^{1}H-NMR (400 MHz, DMSO-d_6 , 120°C) δ: 7.34 (d, 5H), 7.19 (m, br, 1H), 6.73 (d, 2H), 6.60 (s, 1H), 6.53 (d, 2H), 5.01 (s, 2H), 4.70 (m, br, 1H), 4.08 (m, 1H), 3.27 (m, 2H), 3.06 (m, 2H), 2.75 (m, 2H), 2.38 (m, 2H), 2.30 (s, 3H), 2.00- 1.22 (m, 14H).

MS (ES+): 509 $(M+H)^+$.

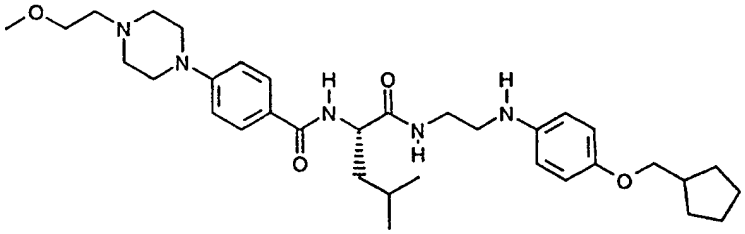
61



^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.09 (d, 1H), 7.96 (t, 1H), 7.78 (d, 2H), 6.94 (d, 2H), 6.70 (d, 2H), 6.51 (d, 2H), 5.08 (t, 1H), 4.45 (m, 1H), 3.60 (d, 2H), 3.48 (t, 2H), 3.26 (s, 3H), 3.26- 3.19 (m, 6H), 3.01 (m, 2H), 2.55 (m, 6H), 1.96 (m, 1H), 1.70- 1.48 (m, 3H), 0.95 (d, 6H), 0.88 (dd, 6H).

MS (ES+): 568 $(M+H)^+$.

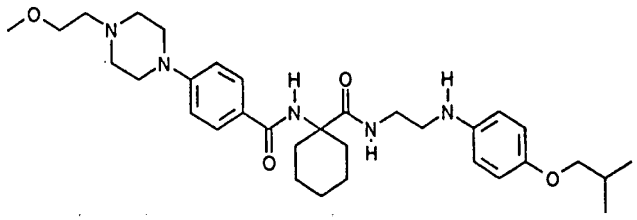
62



^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.09 (d, 1H), 7.96 (t, 1H), 7.39 (d, 2H), 6.93 (d, 2H), 6.70 (d, 2H), 6.50 (d, 2H), 5.09 (t, 1H), 4.45 (m, 1H), 3.70 (d, 2H), 3.49 (t, 2H), 3.28 (s, 3H), 3.22 (m, 4H), 3.00 (m, 2H), 2.55 (m, 4H), 2.51 (t, 2H), 2.22 (m, 1H), 1.78- 1.49 (m, 10H), 1.30 (m, 1H), 0.89 (dd, 6H).

MS (ES+): 594 $(M+H)^+$.

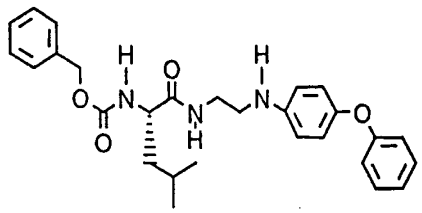
63



^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.78 (d, 2H), 7.57 (s, 1H), 7.49 (t, 1H), 6.96 (d, 2H), 6.68 (d, 2H), 6.50 (d, 2H), 4.91 (m, br, 1H), 3.60 (d, 2H), 3.48 (t, 2H), 3.25 (s, 2H), 3.20 (m, 6H), 3.00 (m, 2H), 2.58 (m, 4H), 2.54 (t, 2H), 2.18- 1.20 (m, 11H), 0.96 (d, 6H).

MS (ES+): 580 $(M+H)^+$.

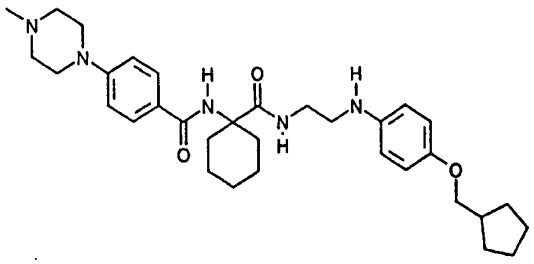
64



mp: 97 – 100°C.

MS (ES+): 476 $(M+H)^+$.

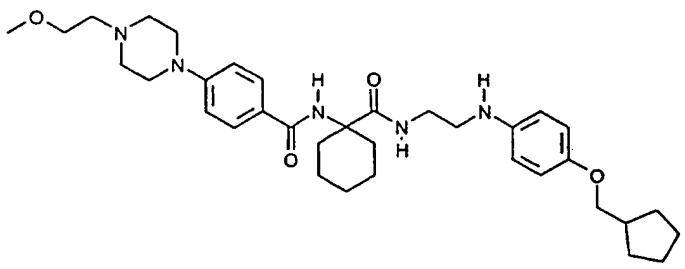
65



^{1}H-NMR (400 MHz, DMSO-d_6, 120°C) δ: 7.77 (d, 2H), 7.32 (t, 1H), 7.30 (s, 1H), 6.92 (d, 2H), 6.69 (d, 2H), 6.50 (d, 2H), 4.71 (m, br, 1H), 3.72 (d, 2H), 3.28 (m, 6H), 3.06 (m, 2H), 2.49 (m, 4H), 2.26 (m, 1H), 2.25 (m, 1H), 2.25 (s, 3H), 2.20- 1.22 (m, 18H).

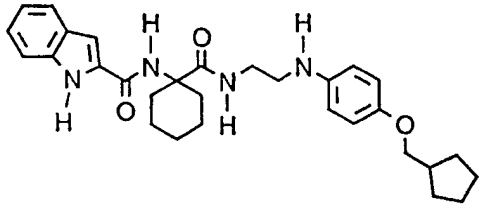
MS (ES+): 562 $(M+H)^+$.

66



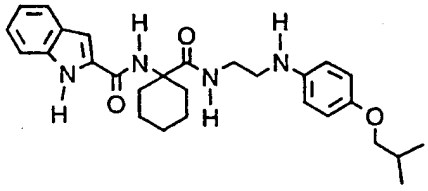
^{1}H-NMR (400 MHz, DMSO-d_6, 120°C) δ: 7.76 (d, 2H), 7.32 (t, 1H), 7.29 (s, 1H), 6.92 (d, 2H), 6.68 (d, 2H), 6.50 (d, 2H), 4.70 (m, br, 1H), 3.72 (d, 2H), 3.50 (t, 2H), 3.30 (s, 3H), 3.27 (m, 6H), 3.05 (m, 2H), 2.59 (m, 6H), 2.25 (m, 1H), 2.17- 1.22 (m, 18H).
MS (ES+): 606 $(M+H)^+$.

67



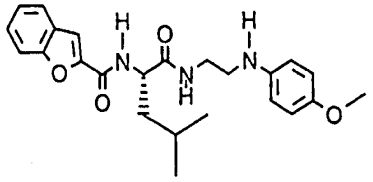
^{1}H-NMR (400 MHz, DMSO-d_6, 120°C) δ: 11.30 (s, 1H), 7.62 (d, 1H), 7.55 (s, 1H), 7.48 (d, 1H), 7.40 (t, 1H), 7.32 (s, 1H), 7.31 (t, 1H), 7.07 (t, 1H), 6.65 (d, 2H), 6.50 (d, 2H), 4.72 (m, br, 1H), 3.72 (d, 2H), 3.28 (m, 2H), 3.08 (m, 2H), 2.02 (m, 1H), 2.17- 1.22 (m, 18H).
MS (ES+): 503 $(M+H)^+$.

68



^{1}H-NMR (300 MHz,$CDCl_3$) δ: 9.48 (s, 1H), 7.65 (d, 1H), 7.44 (d, 1H), 7.32 (t, 1H), 7.15 (t,1H), 6.97 (m, br, 1H), 6.90 (s, 1H), 6.68 (d, 2H), 6.52 (d, 2H), 6.31 (s, 1H), 3.59 (d, 2H), 3.47 (m, 2H), 3.20 (m, 2H), 2.29- 1.30 (m, 1H), 1.00 (d, 6H).
MS (ES+): 477 $(M+H)^+$.

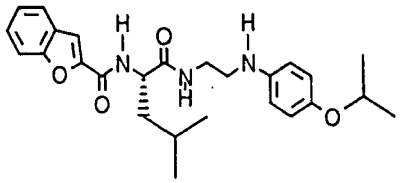
69



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.64 (d, 1H), 7.52 (d, 1H), 7.42 (m, 1H), 7.30 (m, 1H), 7.10 (d, 1H), 6.77 (m, br, 1H), 6.76 (d, 2H), 6.58 (d, 2H), 4.68 (m, 1H), 3.71 (s, 3H), 3.49 (m, 2H), 3.23 (m, 2H), 1.77 (m, 2H), 1.26 (m, 1H), 0.99 (d, 6H).

MS (ES+): 424 $(M+H)^+$.

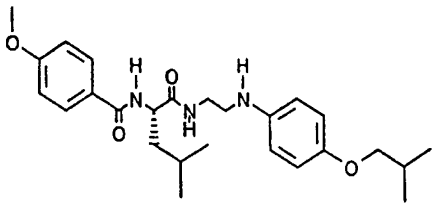
70



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.74 (t, 1H), 7.62 (d, 1H), 7.52- 7.24 (m, 7H), 6.92 (d, 2H), 4.55 (m, 1H), 4.45 (m, 1H), 3.68 (m, 2H), 3.52 (m, 2H), 1.84 (m, 3H), 1.35 (d, 6H), 1.01 (dd, 6H).

MS (ES+): 452 $(M+H)^+$.

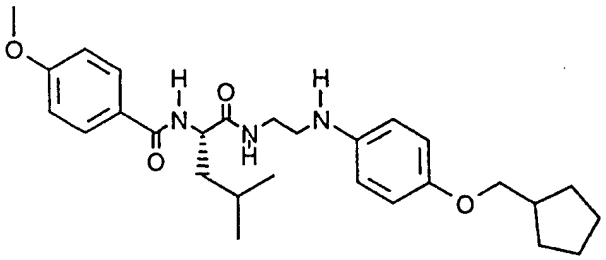
71



mp: 164- 165°C.

MS (ES+): 456 $(M+H)^+$.

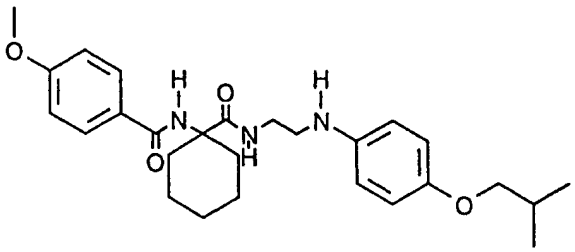
72



mp: 144- 145°C.

MS (ES+): 482 $(M+H)^+$.

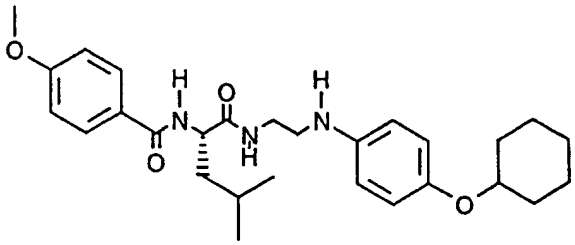
73



mp: 143- 145°C.

MS (ES+):468 $(M+H)^+$.

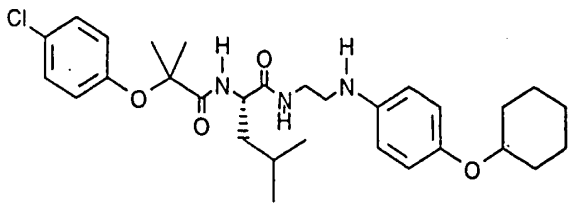
74



mp: 159- 161°C.

MS (ES+):482 $(M+H)^+$.

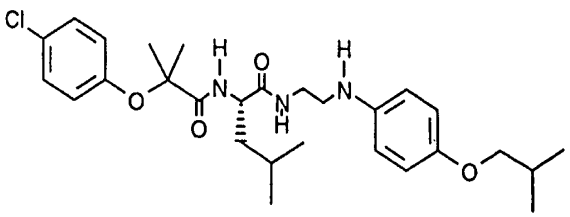
75



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.20 (d, 2H), 6.97 (d, 1H), 6.84 (d, 2H), 6.79 (d, 2H), 6.58 (d, 2H), 6.40 (t, 1H), 4.39 (m, 1H), 4.04 (m, 1H), 3.48 (m, 2H), 3.20 (m, 2H), 2.00- 1.21 (m, 13H), 1.41 (s, 3H), 0.92 (d, 6H).

MS (ES+): 545 $(M+H)^+$.

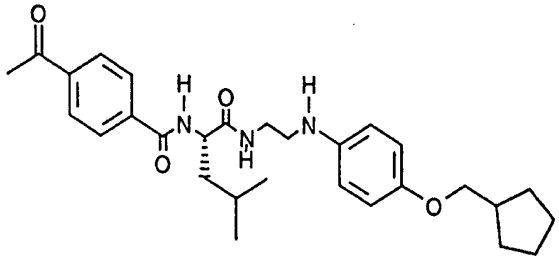
76



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.20 (d, 2H), 6.96 (d, 1H), 6.82 (d, 2H), 6.78 (d, 2H), 6.58 (d, 2H), 6.40 (t, 1H), 4.39 (m, 1H), 3.64 (d, 2H), 3.46 (m, 2H), 3.23 (m, 2H), 2.04 (m, 1H), 1.70 (m, 1H), 1.68 (m, 2H), 1.50 (s, 3H), 1.42 (s, 3H), 1.00 (d, 6H), 0.92 (d, 6H).

MS (ES+): 519 $(M+H)^+$.

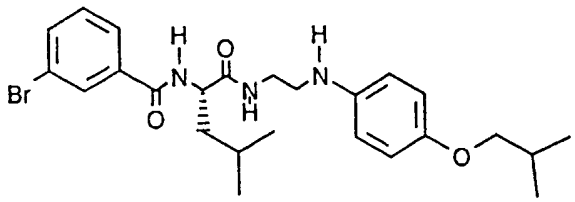
77



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.98 (d, 2H), 7.83 (d, 2H), 6.82 (d, 2H), 6.75 (d, 2H), 6.60 (t, 1H), 6.55 (d, 2H), 4.65 (m, 1H), 3.74 (d, 2H), 3.49 (m, 2H), 3.25 (m, 2H), 2.62 (s, 3H), 2.32 (m, 1H), 1.88- 1.50 (m, 9H), 1.32 (m, 2H), 0.96 (d, 6H).

MS (ES+): 494 $(M+H)^+$.

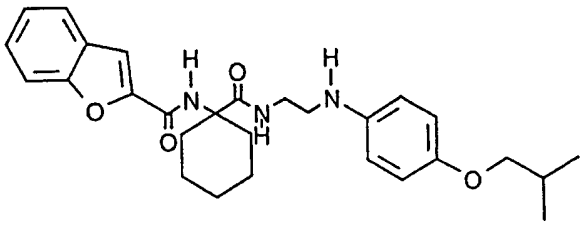
78



^{1}H-NMR (400 MHz, DMSO-d_6, 120°C) δ: 7.90 (d, 1H), 7.70 (m, 1H), 7.50 (s, 1H), 7.40 (m, 1H), 7.36 (m, 2H), 6.72 (d, 2H), 6.52 (d, 2H), 4.80 (m, br, 1H), 4.27 (m, 1H), 3.64 (d, 2H), 3.51 (d, 2H), 3.25 (m, 2H), 3.05 (m, 2H), 1.95 (m, 1H), 1.62- 1.48 (m, 3H), 0.98 (d, 6H), 0.86 (dd, 6H).

MS (ES+): 519 $(M+H)^+$.

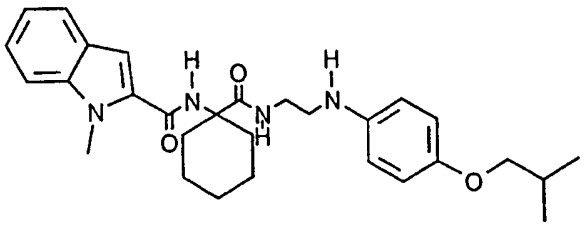
79



^{1}H-NMR (400 MHz,$CDCl_3$) δ: 7.70 (d, 1H), 7.57 (d, 1H), 7.49 (m, 2H), 7.34 (t, 1H), 7.03 (t, 1H), 6.72 (d, 2H), 6.67 (s, 1H), 6.58 (d, 2H), 3.60 (d, 2H), 3.50 (m, 2H), 3.28 (m, 2H), 2.21-1.32 (m, 11H), 1.00 (d, 6H).

MS (H+): 478 $(M+H)^+$.

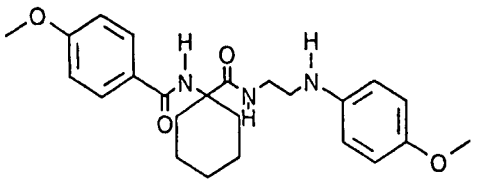
80



^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, 1H), 7.47 (m, 2H), 7.18 (m, 1H), 7.10 (t, 1H), 6.92 (s, 1H), 6.70 (d, 2H), 6.58 (d, 2H), 6.22 (s, 1H), 3.98 (s, 3H), 3.60 (d, 2H), 3.52 (m, 2H), 3.30 (m, 2H), 2.30- 1.25 (m, 11H), 1.01 (d, 6H).

MS (ES+): 491 $(M+H)^+$.

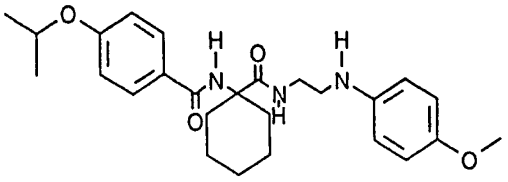
81



mp: 157 – 158°C.

MS (ES+): 426 $(M+H)^+$.

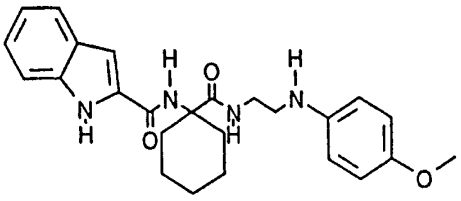
82



mp: 163 – 165°C.

MS (ES+): 454 $(M+H)^+$.

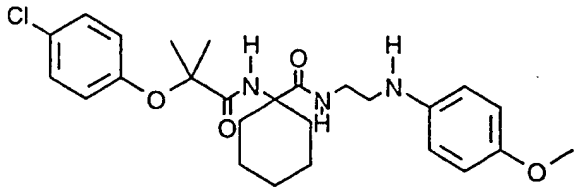
83



mp: 166 – 169°C.

MS (ES+): 435 $(M+H)^+$.

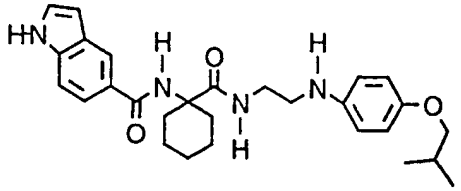
84



mp: 142 – 143°C.

MS (ES+): 489 $(M+H)^+$.

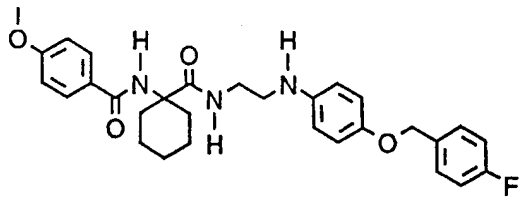
85



^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.53 (s, 1H), 8.10 (s, 1H), 7.65 (d, 1H), 7.44 (d, 1H), 7.32 (m, 1H), 7.30 (m, br, 1H), 6.72 (d, 2H), 6.65 (s, 1H), 6.59 (d, 2H), 6.23 (s, 1H), 3.62 (d, 2H), 3.52 (m, 2H), 3.30 (m, 2H), 2.34- 1.33 (m, 11H), 1.00 (d, 6H).

MS (ES+): 477 $(M+H)^+$.

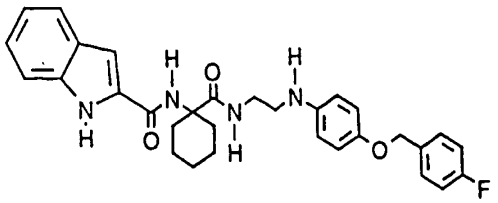
86



^{1}H-NMR (300 MHz, DMSO-d_6) δ: 7.87 (d, 2H), 7.76 (s, 1H), 7.56 (t, 1H), 7.44 (m, 2H), 7.20 (m, 2H), 6.99 (d, 2H), 6.76 (d, 2H), 6.50 (d, 2H), 5.02 (m, 1H), 4.91 (s, 2H), 3.81 (s, 3H), 3.32 (m, 2H), 2.98 (m, 2H), 2.18- 1.20 (m, 10H).

MS (ES+): 520 $(M+H)^+$.

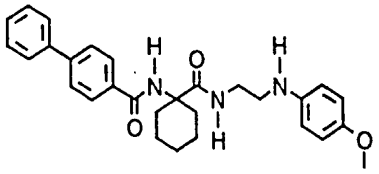
87



^{1}H-NMR (300 MHz, DMSO-d_6) δ: 7.82 (s, 1H), 7.70 (t, 1H), 7.62 (d, 1H), 7.42 (m, 2H), 7.30 (s, 1H), 7.18 (m, 2H), 7.04 (t, 1H), 6.74 (d, 2H), 6.49 (d, 2H), 5.78 (s, 1H), 5.08 (t, 1H), 4.90 (s, 2H), 3.20 (m, 2H), 3.00 (m, 2H), 2.21- 1.19 (m, 10H).

MS (ES+): 529 $(M+H)^+$.

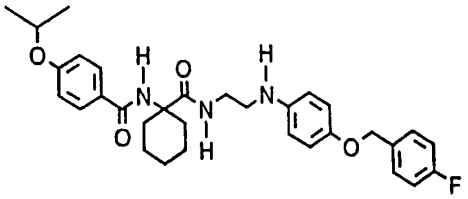
88



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.86 (d, 2H), 7.64 (m, 4H), 7.42 (m, 3H), 7.12 (t, 1H), 6.62 (d, 2H), 6.58 (d, 2H), 6.21 (s, 1H), 3.71 (s, 3H), 3.49 (m, 2H), 3.29 (m, 2H), 2.30- 1.28 (m, 10H).

MS (ES+): 472 $(M+H)^+$.

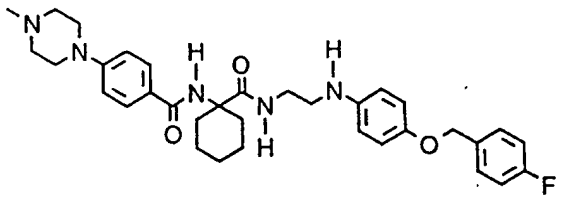
89



mp: 177 – 179°C.

MS (ES+): 548 $(M+H)^+$.

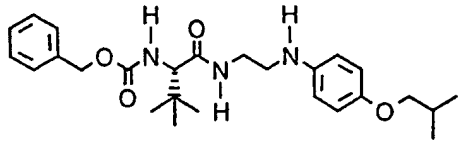
90



mp: 181 – 183°C.

MS (ES+): 588 $(M+H)^+$.

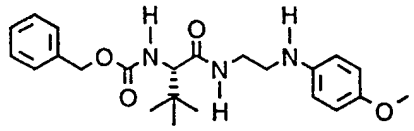
91



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.31 (s, 5H), 6.72 (d, 2H), 6.65 (m, br, 1H), 6.54 (d, 2H), 5.71 (d, 1H), 5.02 (s, 2H), 3.96 (d, 1H), 3.59 (d, 2H), 3.40 (m, 2H), 3.19 (m, 2H), 1.24 (m, 1H), 1.00 (s, 9H), 0.98 (d, 6H).

MS (ES+): 456 $(M+H)^+$.

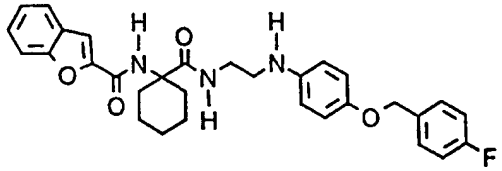
92



^{1}H-NMR (300 MHz,$CDCl_3$) δ: 7.30 (s, 5H), 6.74 (d, 2H), 6.66 (m, br, 1H), 6.54 (d, 2H), 5.71 (d, 1H), 5.04 (s, 2H), 3.97 (d, 1H), 3.74 (s, 3H), 3.40 (m, 2H), 3.18 (m, 2H), 1.00 (s, 9H).

MS (ES+): 414 $(M+H)^+$.

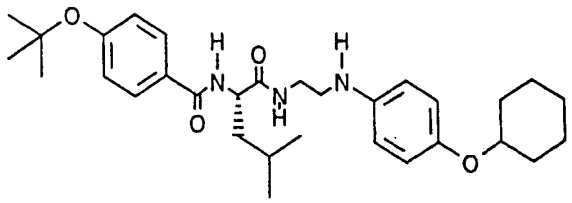
93



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.70 (d, 2H), 7.57- 7.30 (m, 6H), 7.04 (m, 3H), 6.76 (d, 2H), 6.66 (s, 1H), 6.58 (d, 2H), 4.89 (s, 2H), 3.50 (m, 2H), 3.23 (m, 2H), 2.32- 1.34 (m, 10H).

MS (ES+): 530 $(M+H)^+$.

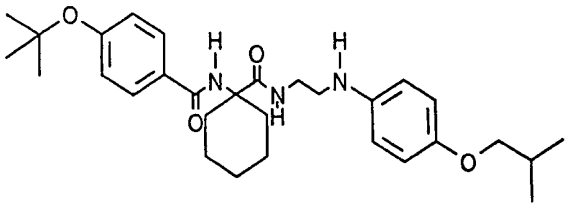
94



mp: 130 – 132°C.

MS (ES+): 524 $(M+H)^+$.

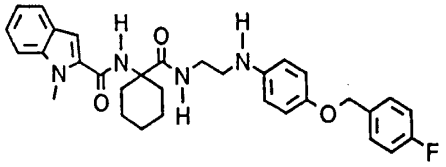
95



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.70 (d, 2H), 7.20 (m, br, 1H), 7.02 (d, 2H), 6.76 (d, 2H), 6.65 (d, 2H), 6.19 (s, 1H), 3.63 (d, 2H), 3.50 (m, 2H), 3.28 (m, 2H), 2.29- 1.42 (m, 13H), 1.39 (s, 9H), 1.00 (d, 6H).

MS (ES+): 510 $(M+H)^+$.

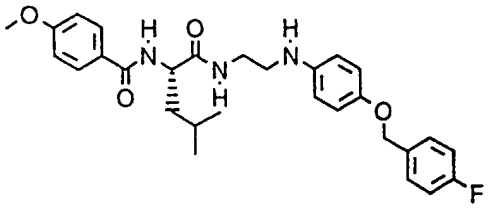
96



mp: 162 – 164°C.

MS (ES+): 543 $(M+H)^+$.

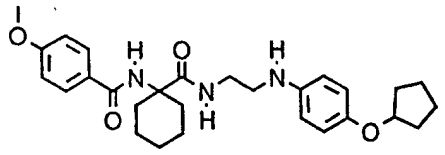
97



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.78 (d, 2H), 7.48- 6.75 (m, 11H), 4.92 (s, 2H), 4.60 (m, 1H), 3.83 (s, 3H), 3.61 (m, 2H), 3.35 (m, 2H), 1.70 (m, 2H), 1.20 (m, 1H), 0.92 (d, 6H).

MS (ES+): 508 $(M+H)^+$.

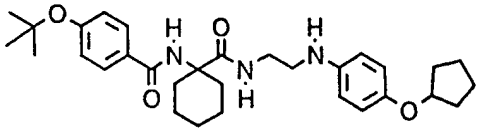
98



mp: 149 – 150°C.

MS (ES+): 480 $(M+H)^+$.

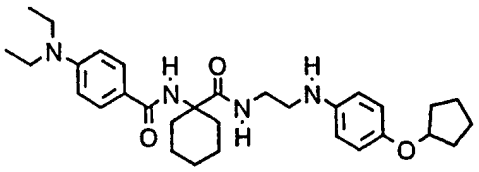
99



mp: 153– 154°C.

MS (ES+): 522 $(M+H)^+$.

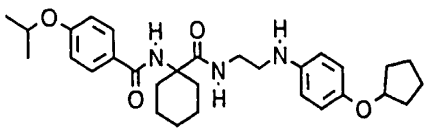
100



mp: 174– 175°C.

MS (ES+): 521 $(M+H)^+$.

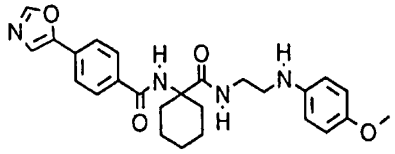
101



mp: 121– 122°C.

MS (ES+): 508 $(M+H)^+$.

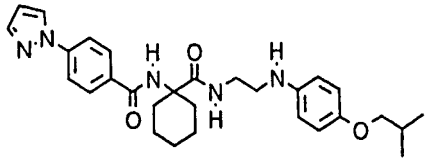
102



mp: 169– 171°C.

MS (ES+): 463 $(M+H)^+$.

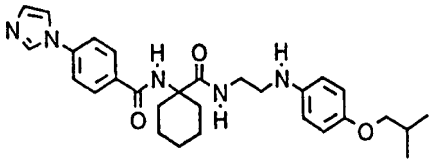
103



mp: 152- 154°C.

MS (ES+): 504 $(M+H)^+$.

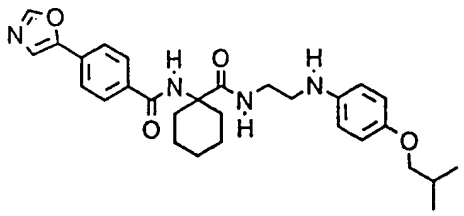
104



mp: 210- 211°C.

MS (ES+): 504 $(M+H)^+$.

105

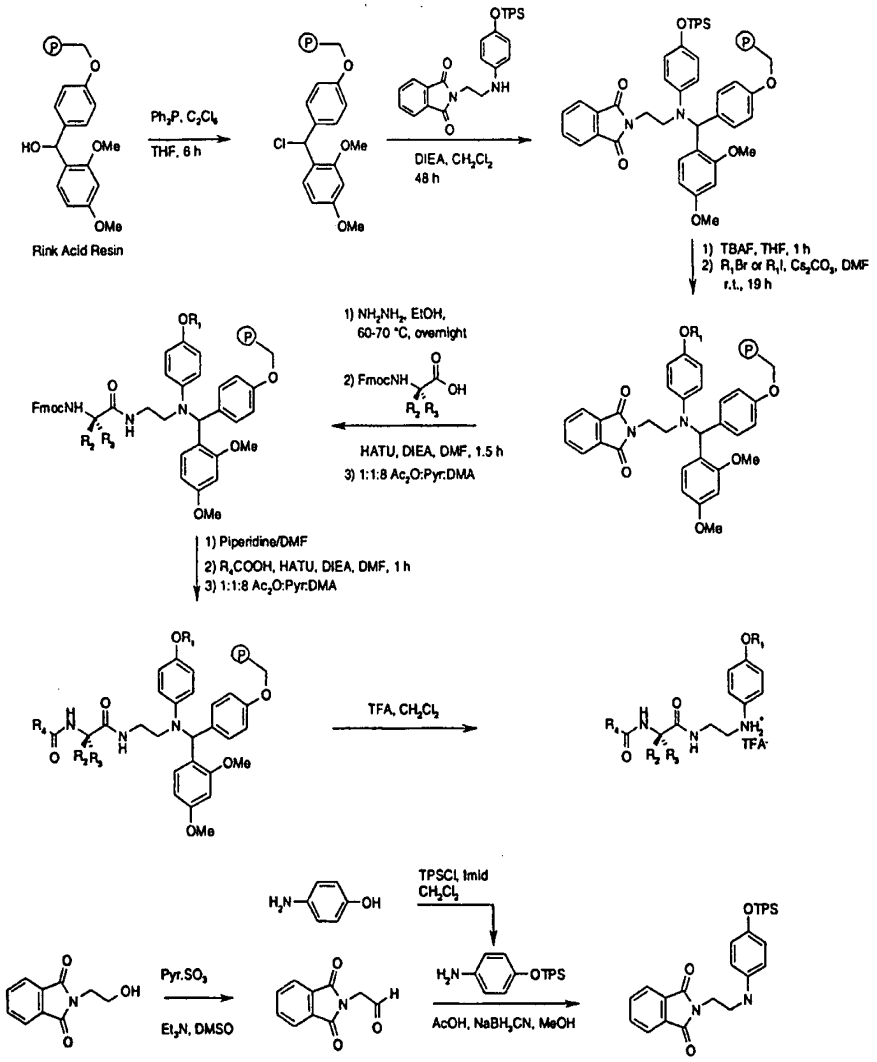


mp: 167- 177°C.

MS (ES+): 505 $(M+H)^+$.

Alternatively the Compounds of the invention may be synthesised using solid phase chemistry. The reaction scheme for synthesis of typical arylaminoethyl amides is given below together with the experimental procedures used, including procedures for a variety of Ar substituents.

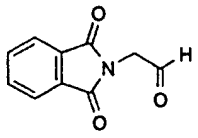
Synthesis of Arylamines on Solid Support.



Experimental Procedures

Rink chloride resin is prepared according to a reported literature procedure. See: Garigipati, R. S. Tetrahedron Lett. **1997**, *38*, 6807.

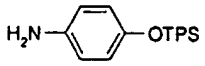
Synthesis of *N*-2-Oxo-Ethyl-Phthalimide



To a solution of alcohol (57.36 g, 0.3 mol) and Et_3N (209 mL, 1.5 mol) in DMSO (750 mL) is added solid Pyr.SO_3 (143.3 g, 0.9 mol) by portions. The resultant mixture is stirred at room temperature for 1 h.

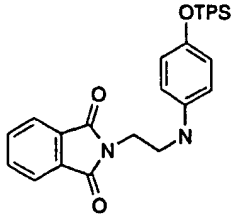
The reaction mixture is poured into a mixture of CH_2Cl_2 and 0.5 N aq citric acid. The layers are separated and the organic layer is washed with H_2O and brine. The organic phase is dried (Na_2SO_4), and the solvent is removed *in vacuo*. The resultant residue is purified by flash chromatography (2:1 toluene:EtOAc) to provide *N*-2-oxo-ethyl-phthalimide as a white solid.

Synthesis of 4-(*tert*-Butyldiphenylsilanyloxy)phenylamine



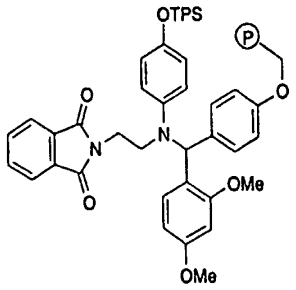
To a suspension of 4-aminophenol (2.2 g, 20.2 mmol) and imidazole (1.78 g, 26.2 mmol) in CH_2Cl_2 (50.5 mL) is added TPSCl (6.2 mL, 24.2 mmol). The resultant suspension is stirred at r.t. for 15 h. After diluting the mixture with CH_2Cl_2 (100 mL), H_2O (100 mL) is added. The layers are separated. The organic phase is washed with brine, dried ($MgSO_4$) and the solvent is removed *in vacuo*. The residue is purified by flash chromatography (4:1 hexanes:EtOAc) to provide 4-(*tert*-butyldiphenylsilanyloxy)phenylamine as an oil.

Synthesis of 2-{2-[4-(*tert*-Butyldiphenylsilanyloxy)-phenylamino]-ethyl}-isoindole-1,3-dione



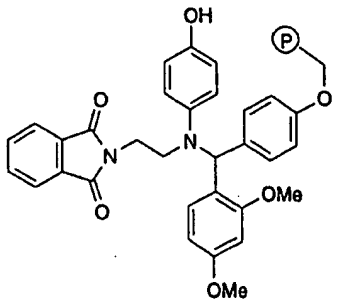
To a solution of *N*-2-oxo-ethyl-phthalimide (2.77 g, 14.65 mmol) and of 4-(*tert*-butyldiphenylsilanyloxy)phenylamine (3.92 g, 11.3 mmol) in MeOH (100 mL) is added AcOH (966 mL, 16.90 mmol). The resultant solution is stirred for 30 min at room temperature. A solution of $NaBH_3CN$ (354.1 mg, 5.64 mmol) in MeOH (10 mL) is added slowly to the reaction mixture. After stirring the mixture at r.t. for 3 h, the solution is poured into sat. aq NH_4Cl. The solvents are removed *in vacuo*. The residue is dissolved in AcOEt/sat. aq NH_4Cl. The layers are separated and the aqueous phase is extracted once more with AcOEt. The combined organic layers are washed with brine, dried (Na_2SO_4) and the solvent is removed *in vacuo*. The residue is purified by flash chromatography (8:2 hexanes:AcOEt) to provide of 2-{2-[4-(*tert*-butyl-diphenylsilanyloxy)-phenylamino]-ethyl}-isoindole-1,3-dione as a yellow solid that is recrystallized from ether:hexane.

Loading of 2-{2-[4-(*tert*-butyldiphenylsilanyloxy)-phenylamino]-ethyl}-isoindole-1,3-dione on Rink resin



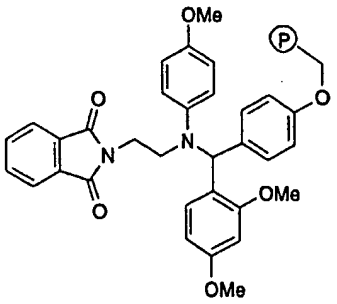
A flame-dried fritted flask (equipped with a valve) under N_2 is charged with Rink chloride resin (10.68 g, 5.55 mmol) and CH_2Cl_2 (100 mL). To the resulting suspension are added successively DIEA (3.5 mL, 20 mmol) and a solution of 2-{2-[4-(*tert*-butyldiphenylsilanyloxy)-phenylamino]-ethyl}-isoindole-1,3-dione (7.22 g, 13.9 mmol) in CH_2Cl_2 (30 mL). The mixture is shaken for 67 h under N_2. The resin is then filtered, washed with CH_2Cl_2, MeOH, CH_2Cl_2, MeOH and CH_2Cl_2 (3 times each) and dried *in vacuo*.

Removal of the *tert*-Butyldiphenylsilyl Protecting Group



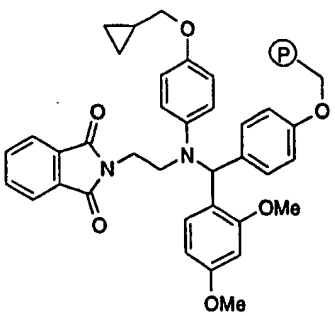
To a suspension of resin (5.55 mmol) in THF (110 mL) is added a solution of TBAF in THF (1 M, 11.0 mmol). The resultant suspension is shaken for 1.5 h at r.t. The resin is filtered, and then washed with THF, 1:1 THF:H_2O, H_2O, 1:1 THF:H_2O, THF and MeOH (3 times each). The resin is coevaporated with toluene twice and dried *in vacuo* at 40 °C.

Preparation of the Methylether



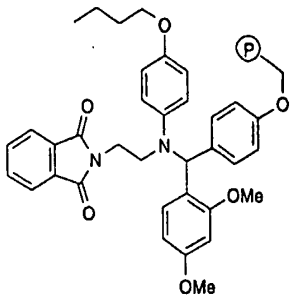
To a suspension of alcohol resin (0.624 mmol) in anhydrous DMF (67 mL) are added successively Cs_2CO_3 (0.92 g, 2.81 mmol) and methyl iodide (0.195 mL, 3.12 mmol). The resultant suspension is shaken at r.t. for 17 h. The resin is filtered and then washed with DMF, H_2O, 1:1 THF:H_2O, THF, CH_2Cl_2 and MeOH (3 times each). The resin is dried *in vacuo*.

Preparation of the Cyclopropylmethylether



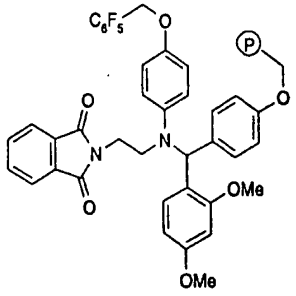
To a suspension of alcohol resin (0.728 mmol) in anhydrous DMF (67 mL) are added successively Cs_2CO_3 (1.07 g, 3.28 mmol) and (bromomethyl)cyclopropane (0.348 mL, 3.64 mmol). The resultant suspension is shaken at r.t. for 17 h. The resin is filtered and then washed with DMF, H_2O, 1:1 THF:H_2O, THF, CH_2Cl_2 and MeOH (3 times each). The resin is dried *in vacuo*.

Preparation of the Butylether



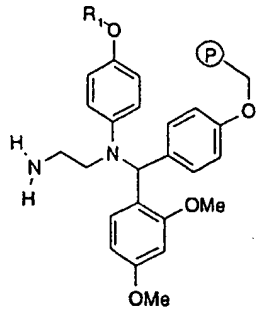
To a suspension of alcohol resin (0.728 mmol) in anhydrous DMF (67 mL) are added successively Cs_2CO_3 (1.07 g, 3.28 mmol) and *n*-butyl bromide (0.392 mL, 3.64 mmol). The resultant suspension is shaken at r.t. for 17 h. The resin is filtered and then washed with DMF, H_2O, 1:1 THF:H_2O, THF, CH_2Cl_2 and MeOH (3 times each). The resin is dried *in vacuo*.

Preparation of the Pentafluorophenylmethylether



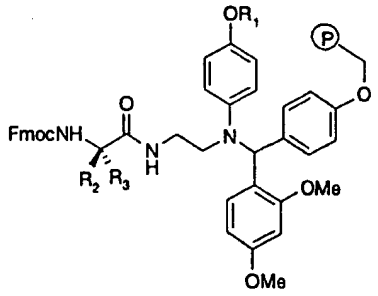
To a suspension of alcohol resin (0.728 mmol) in anhydrous DMF (67 mL) are added successively Cs_2CO_3 (1.07 g, 3.28 mmol) and bromomethylpentafluorobenzene (0.512 mL, 3.64 mmol). The resultant suspension is shaken at r.t. for 17 h. The resin is filtered and then washed with DMF, H_2O, 1:1 THF:H_2O, THF, CH_2Cl_2 and MeOH (3 times each). The resin is dried *in vacuo*.

Hydrazine Deprotection: general procedure



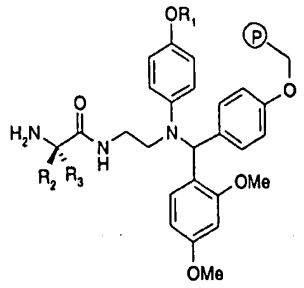
To a suspension of resin (0.624 mmol) in EtOH (25 mL) is added $NH_2NH_2.H_2O$ (0.777 mL, 25.0 mmol). The resultant suspension is shaken at 60 °C for 17 h. The reaction mixture is cooled to r.t. and the resin is filtered. The resin is washed with 1:1 THF:H_2O, H_2O, 1:1 THF:H_2O, THF, CH_2Cl_2 and MeOH (3 times each). The resin is then dried *in vacuo*.

Coupling procedure: general procedure



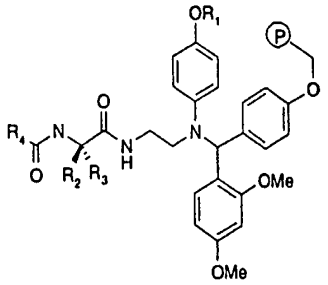
A solution of Fmoc amino acid (0.086 mmol), HATU (0.086 mmol) and DIEA (0.213 mmol) in DMF (1.6 mL) is shaken for 10 min prior to addition to the resin (0.043 mmol). The resultant suspension is shaken for 1.5 h at r.t. The resin is allowed to settle down and the supernatant is then removed. The resin is washed with DMA, *i*-propanol and dichloroethane (3 times each) and dried. The resin is then treated with a 1:1:8 Ac_2O:Pyr:DMA solution (1.5 mL) for 10 min. The supernatant is removed and the resin is washed with DMA, *i*-propanol and dichloroethane (3 times each). The resin is dried *in vacuo* at 40 °C for 30 min.

Fmoc removal: general procedure



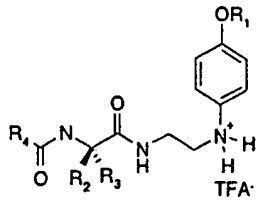
The resin is treated with a 20% solution of piperidine in DMF (1.5 mL) for 5 min. The supernatant is then removed and the resin is washed with DMF, MeOH, THF and CH_2Cl_2. The procedure is repeated 8 times.

Coupling procedure: general procedure



A solution of acid (0.086 mmol), HATU (0.086 mmol) and DIEA (0.213 mmol) in DMF (1.5 mL) is shaken for 10 min prior to addition to the resin (0.043 mmol). The resultant suspension is shaken for 1.5 h at r.t. The resin is allowed to settle and the supernatant is then removed. The resin is washed with DMF, THF, CH_2Cl_2, MeOH, CH_2Cl_2 and MeOH (3 times each) and dried. The resin is then treated with a 1:1:8 Ac_2O:Pyr:DMA solution (1.5 mL) for 10 min. The supernatant is removed and the resin is washed with DMF, MeOH and CH_2Cl_2 (3 times each). The above procedure is repeated once more, the supernatant is removed and the resin is washed with DMF, THF, CH_2Cl_2, MeOH, CH_2Cl_2 and MeOH (3 times each). The resin is dried *in vacuo* at 40 °C overnight.

Cleavage of the 2-(4-alkoxyphenylamino)ethyl amide derivatives from the solid support: general procedure

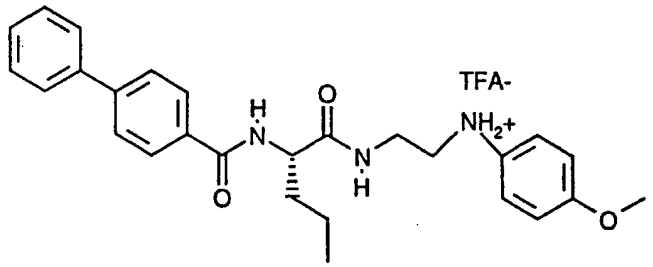


A suspension of resin (0.0426 mmol) in 20% (95% TFA:H_2O)/CH_2Cl_2 (1.5 mL) is shaken at r.t. for 15 min. The resin is filtered and the filtrate collected. The solvent is removed *in vacuo*. The residue is purified by reverse phase HPLC (Macherey-Nagel C18, 125 mm x 20 mm; gradient: 10:90 to 100:0 CH_3CN + 0.1% TFA : H_2O + 0.1% TFA over 16 min, then 2.5 min 100% CH_3CN + 0.1% TFA ; rate of elution: 15 mL/min).

Compounds of the Invention synthesised using solid phase procedures are given below in Example 106 to 113 together with their spectral data.

Example Number Compound

106

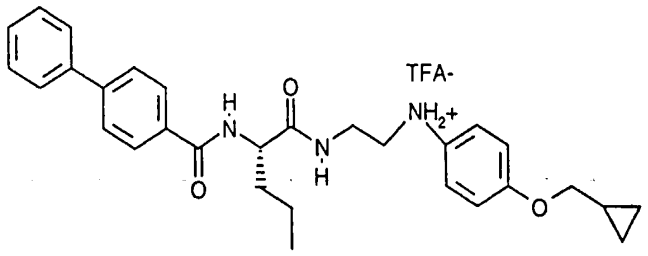


IR (film) ν max: 3291, 3061, 3031, 2963, 2936, 2875, 2840, 1672, 1541, 1514, 1486, 1447, 1307, 1259, 1203, 1183, 1032, 835, 799, 748, 721, 698 cm^{-1}.

^1H NMR (400 MHz, CD_3OD) δ: 7.99 (d, 2H, *J* = 8.5 Hz), 7.76 (d, 2H, *J* = 8.5 Hz), 7.69 (d, 2H, *J* = 8.5 Hz), 7.53-7.33 (m, 5H), 7.06 (d, 2H, *J* = 8.5 Hz), 4.44 (t, 1H, *J* = 7.5 Hz), 3.84 (s, 3H), 3.77-3.63 (m, 1H), 3.60-3.40 (m, 3H), 1.89 (dt, 2H, *J* = 7.5, 7.5 Hz), 1.63-1.41 (m, 2H), 1.03 (t, 3H, *J* = 7.5 Hz).

MS (ES+) *m/z* 446 $(M+H)^+$, 891 $(2M + H)^+$.

107

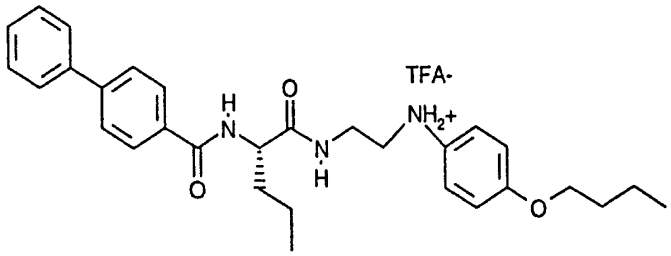


IR (film) ν max: 3295, 3064, 3030, 2962, 2935, 2875, 1671, 1540, 1512, 1486, 1254, 1202, 1137, 1025, 1008, 855, 834, 799, 748, 721, 698 cm^{-1}.

^1H NMR (400 MHz, CD_3OD) δ: 7.98 (d, 2H, *J* = 8.5 Hz), 7.76 (d, 2H, *J* = 8.5 Hz), 7.69 (d, 2H, *J* = 8.5 Hz), 7.53-7.33 (m, 5H), 7.05 (d, 2H, *J* = 8.5 Hz), 4.43 (t, 1H, *J* = 7.5 Hz), 3.86 (d, 2H, *J* = 7.0 Hz), 3.76-3.65 (m, 1H), 3.63-3.53 (m, 1H), 3.52-3.42 (m, 2H), 1.89 (dt, 2H, *J* = 7.5, 7.5 Hz), 1.64-1.42 (m, 2H), 1.30-1.20 (m, 1H), 1.03 (t, 3H, *J* = 7.5 Hz), 0.68-0.60 (m, 2H), 0.39-0.32 (m, 2H).

MS (ES+) *m/z* 486 $(M+H)^+$, 508 $(M + Na)^+$, 971 $(2M + H)^+$.

108



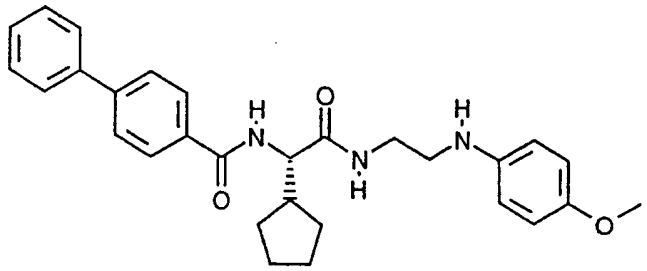
IR (film) ν max: 3291, 3061, 3032, 2961, 2935, 2874, 1671, 1541, 1512, 1486, 1307, 1257, 1202, 1137, 855, 834, 799, 748, 721, 697 cm^{-1}.

^1H NMR (400 MHz, CD_3OD) δ: 7.99 (d, 2H, *J* = 8.5 Hz), 7.76 (d, 2H, *J* = 8.5 Hz), 7.69 (dd, 2H, *J* = 1.0, 8.5 Hz), 7.52-7.37 (m, 5H), 7.07 (d, 2H, *J* = 8.5 Hz), 4.43 (t, 1H, *J* = 7.5 Hz), 4.02 (t,

2H, J = 6.5 Hz), 3.77-3.68 (m, 1H), 3.64-3.55 (m, 1H), 3.54-3.42 (m, 2H), 1.89 (dt, 2H, J = 7.5, 7.5 Hz), 1.82-1.73 (m, 2H), 1.61-1.41 (m, 4H), 1.04 (t, 3H, J = 7.5 Hz), 1.00 (t, 3H, J = 7.5 Hz).

MS (ES+) *m/z* 488 $(M+H)^+$, 975 $(2M + H)^+$.

109

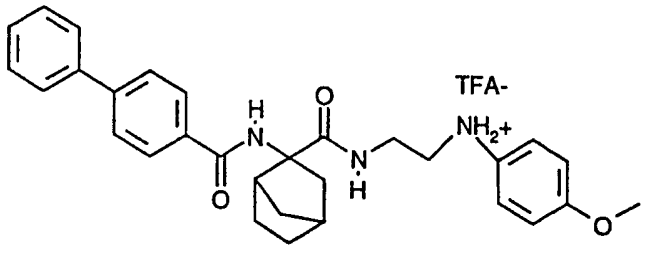


IR (film) ν max: 3397, 3301, 3057, 3033, 2954, 2861, 1640, 1618, 1582, 1558, 1516, 1486, 1450, 1428, 1262, 1238, 1201, 1179, 1137, 1039, 981, 816, 744, 694 cm^{-1}.

^1H NMR (400 MHz, CD_3OD) δ: 7.99 (d, 2H, J = 8.5 Hz), 7.76 (d, 2H, J = 8.5 Hz), 7.69 (d, 2H, J = 8.5 Hz), 7.53-7.33 (m, 5H), 7.06 (d, 2H, J = 8.5 Hz), 4.24 (d, 1H, J = 10.0 Hz), 3.83 (s, 3H), 3.80-3.70 (m, 1H), 3.64-3.52 (m, 1H), 3.51-3.39 (m, 2H), 2.48-2.35 (m, 1H), 2.10-1.97 (m, 1H), 1.84-1.59 (m, 5H), 1.52-1.38 (m, 2H).

MS (ES+) *m/z* 472 $(M+H)^+$, 943 $(2M + H)^+$.

110

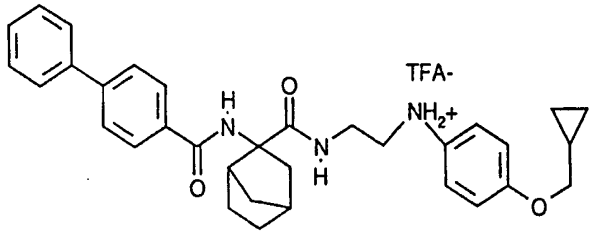


IR (film) ν max: 3307, 3030, 2961, 2936, 2875, 2839, 1671, 1581, 1513, 1484, 1448, 1425, 1307, 1259, 1202, 1136, 1032, 1008, 833, 798, 749, 721, 698 cm^{-1}.

^1H NMR (400 MHz, CD_3OD) δ: 7.97 (d, 2H, *J* = 8.5 Hz), 7.76 (d, 2H, *J* = 8.5 Hz), 7.69 (d, 2H, *J* = 8.5 Hz), 7.52-7.37 (m, 5H), 7.05 (d, 2H, *J* = 9.0 Hz), 3.84 (s, 3H), 3.71-3.60 (m, 1H), 3.58-3.37 (m, 3H), 3.11 (br s, 1H), 2.32 (br s, 1H), 2.29-2.19 (m, 1H), 1.91 (d, 1H, *J* = 10.0 Hz), 1.75 (dd, 1H, *J* = 3.0, 13.5 Hz), 1.72-1.44 (m, 5H).

MS (ES+) *m/z* 484 $(M+H)^+$, 506 $(M + Na)^+$, $(2M + H)^+$ 967.

111

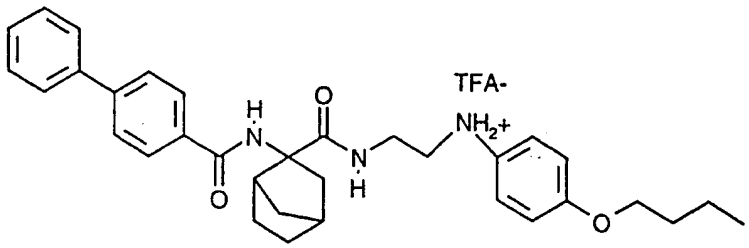


IR (film) ν max: 3306, 2961, 2875, 1671, 1533, 1512, 1484, 1449, 1426, 1306, 1254, 1202, 1136, 1025, 1008, 833, 799, 749, 721, 698 cm^{-1}.

^1H NMR (400 MHz, CD_3OD) δ: 8.71 (s, 1H), 7.97 (d, 2H, *J* = 8.5 Hz), 7.76 (ddd, 2H, *J* = 2.0, 2.0, 8.5 Hz), 7.69 (d, 2H, *J* = 8.5 Hz), 7.52-7.37 (m, 5H), 7.04 (d, 2H, *J* = 8.5 Hz), 3.86 (d, 2H, *J* = 7.0 Hz), 3.71-3.60 (m, 1H), 3.59-3.37 (m, 3H), 3.10 (d, 1H, *J* = 2.0 Hz), 2.32 (br s, 1H), 2.22 (dm, 1H, *J* for d = 10.0 Hz), 1.91 (d, 1H, *J* = 10.0 Hz), 1.75 (dd, 1H, *J* = 3.0, 13.5 Hz), 1.72-1.44 (m, 5H), 1.30-1.20 (m, 1H), 0.67-0.58 (m, 2H), 0.38-0.32 (m, 2H).

MS (ES+) *m/z* 524 (M+H).

112

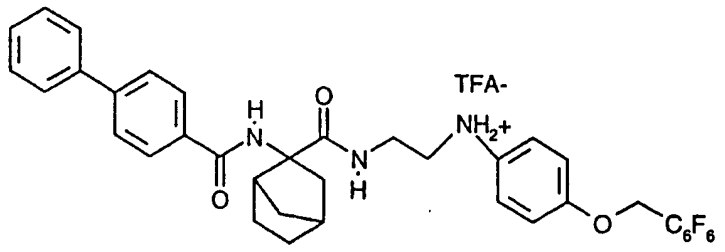


IR (film) ν max: 3311, 3057, 3031, 2960, 2874, 1671, 1535, 1512, 1484, 1449, 1429, 1307, 1257, 1202, 1177, 1136, 1065, 1034, 1008, 833, 798, 749, 721, 698 cm^{-1}.

^1H NMR (400 MHz, CD_3OD) δ: 7.97 (d, 2H, *J* = 8.5 Hz), 7.76 (d, 2H, *J* = 8.5 Hz), 7.69 (d, 2H, *J* = 8.5 Hz), 7.52-7.38 (m, 5H), 7.06 (d, 2H, *J* = 9.0 Hz), 4.02 (t, 2H, *J* = 6.5 Hz), 3.72-3.61 (m, 1H), 3.59-3.40 (m, 3H), 3.10 (d, 1H, *J* = 2.5 Hz), 2.32 (br s, 1H), 2.22 (dm, 1H, *J* for d = 10.0 Hz), 1.91 (d, 1H, *J* = 10.0 Hz), 1.82-1.72 (m, 3H), 1.72-1.60 (m, 2H), 1.60-1.44 (m, 5H), 1.00 (t, 3H, *J* = 7.5 Hz).

MS (ES+) *m/z* 526 $(M+H)^+$, 1051 $(2M + H)^+$.

113



IR (film) ν max: 3305, 3032, 2963, 2877, 1610, 1523, 1510, 1485, 1427, 1392, 1310, 1248, 1202, 1134, 1058, 1020, 1009, 976, 942, 855, 833, 799, 750, 721, 698 cm^{-1}.

^1H NMR (400 MHz, CD_3OD) δ: 8.71 (s, 1H), 7.97 (d, 2H, *J* = 8.5 Hz), 7.76 (d, 2H, *J* = 8.5 Hz), 7.68 (d, 2H, *J* = 8.5 Hz), 7.52-7.38 (m, 5H), 7.16 (d, 2H, *J* = 9.0 Hz), 5.23 (s, 2H), 3.73-3.60 (m,

1H), 3.60-3.38 (m, 3H), 3.10 (br s, 1H), 2.32 (br.s, 1H), 2.28-2.20 (m, 1H), 1.91 (d, 1H, J = 10.0 Hz), 1.75 (dd, 1H, J = 3.0, 13.5 Hz), 1.72-1.43 (m, 6H).

MS (ES+) m/z 650 $(M+H)^+$.

Further Compounds of the Invention (Examples 114 to) are prepared by solution phase chemistry involving coupling of various 4-substituted benzoic acid derivatives with 1-amino-cyclohexane carboxylic acid [2-(4-methoxy-phenylamino)-ethyl]-amide; as described below for the preparation of 4-isopropyl-N-{1-[2-(4-methoxy-phenylamino)-ethylcarbamoyl]-cyclohexyl}-benzamide.

Example 114: 4-isopropyl-.N.-{1-[2-(4-methoxy-phenylamino)-ethylcarbamoyl]-cyclohexyl}-benzamide.

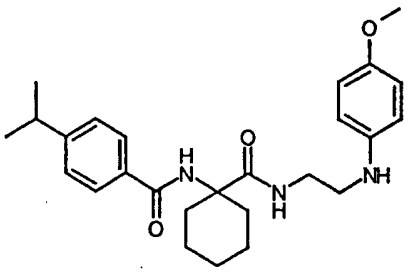
To a solution of 4-isopropyl-benzoic acid (2.53 g, 15.4 mmol) in DMF (20 mL) are added successively DIEA (9.4 mL, 53.96 mmol) and HATU (7.61 g, 20.02 mmol). The resultant mixture is stirred at r.t. for 10 min, prior to being added to a solution of 1-amino-cyclohexanecarboxylic acid [2-(4-methoxy-phenylamino)-ethyl]-amide (4.49 g, 15.40 mmol) in DMF (57 mL). The reaction mixture is stirred at r.t for 1.5 h. Most of the solvent is removed *in vacuo*. The residue is dissolved in AcOEt and washed with sat. aq $NaHCO_3$, H_2O and brine. The organic layer is dried ($MgSO_4$) and the solvent is removed in vacuo. The residue is purified by flash chromatography (1:1:1 Hexanes:CH_2Cl_2:AcOEt) to furnish a solid. Recristallization from AcOEt:hexanes or AcOEt:CH_2Cl_2:hexanes provides 4-isopropyl-.N.-{1-[2-(4-methoxy-phenylamino)-ethylcarbamoyl]-cyclohexyl}-benzamide as a colourless cristalline material.

HATU = O-(7-azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluorophosphate.

Other 4-substituted benzoic acid derivatives are coupled in an analogous manner.

Example Number Compound

115

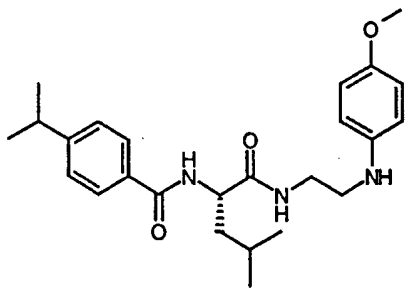


IR (KBr) ν max: 3302, 2963, 2938, 2853, 1649, 1518, 1441, 1312, 1248, 1033, 850, 817 cm^{-1}.

^1H NMR (400 MHz, CD_3SOCD_3) δ: 7.82 (s, 1H), 7.81 (d, 2H, *J* = 8.0 Hz), 7.57 (t, 1H, *J* = 6.0 Hz), 7.33 (d, 2H, *J* = 8.0 Hz), 6.69 (d, 2H, *J* = 8.8 Hz), 6.51(d, 2H, *J* = 8.8 Hz), 4.98 (t, 1H, *J* = 6.0 Hz), 3.63 (s, 3H), 3.22 (dt, 2H, *J* = 6.0, 6.0 Hz), 3.03-2.91 (m, 3H), 2.18-2.09 (m, 2H), 1.80-1.68 (m, 2H), 1.60-1.43 (m, 5H), 1.32-1.16 (m, 1H), 1.23 (d, 6H, *J* = 7.0 Hz).

MS (ES+) *m/z* 438 $(M+H)^+$, 875 $(2M+H)^+$.

116

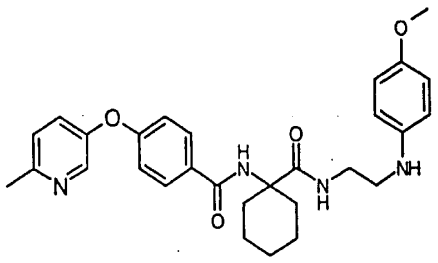


IR (KBr) ν max: 3360, 3340, 3304, 2959, 1656, 1630, 1527, 1329, 1236, 1136, 849, 815 cm^{-1}.

^1H NMR (400 MHz, CD_3SOCD_3) δ: 8.37 (d, 1H, *J* = 8.0 Hz), 8.04 (t, 1H, *J* = 6.0 Hz) 7.86 (d, 2H, *J* = 8.0 Hz), 7.34 (d, 2H, *J* = 8.0 Hz), 6.71 (d, 2H, *J* = 8.8 Hz), 6.54 (d, 2H, *J* = 8.8 Hz), 5.14 (partly resolved t, 1H), 4.53-4.43 (m, 1H), 3.64 (s, 3H), 3.23 (dt, 2H, *J* = 6.0, 6.0 Hz), 3.07-2.98 (m, 2H), 2.96 (sept, 1H, *J* = 7.0 Hz), 1.75-1.49 (m, 3H), 1.23 (d, 6H, *J* = 7.0 Hz), 0.91 (d, 3H, *J* = 6.0 Hz), 0.87 (d, 3H, *J* = 6.0 Hz).

MS (ES+) *m/z* 426 $(M+H)^+$, 851 $(2M+H)^+$.

117

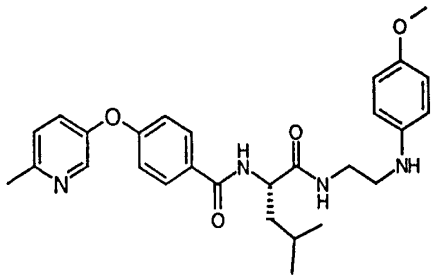


IR (KBr) ν max: 3389, 3331, 3269, 2945, 1647, 1623, 1581, 1537, 1512, 1498, 1480, 1234, 1173, 817 cm^{-1}.

^1H NMR (400 MHz, CD_3SOCD_3) δ: 8.30 (d, 1H, *J* = 2.8 Hz), 7.93 (d, 2H, *J* = 8.5 Hz), 7.90 (s, 1H), 7.60 (t, 1H, *J* = 6.0 Hz), 7.44 (dd, 1H, *J* = 2.8, 8.5 Hz), 7.34 (d, 1H, *J* = 8.5 Hz), 7.07 (d, 2H, *J* = 8.8 Hz), 6.70 (d, 2H, *J* = 8.8 Hz), 6.52 (d, 2H, *J* = 8.8 Hz), 4.99 (t, 1H, *J* = 6.0 Hz), 3.63 (s, 3H), 3.22 (dt, 2H, *J* = 6.0, 6.0 Hz), 2.99 (dt, 2H, *J* = 6.0, 6.0 Hz), 2.50 (s, 3H), 2.18-2.08 (m, 2H), 1.81-1.69 (m, 2H), 1.62-1.43 (m, 5H), 1.32-1.17 (m, 1H).

MS (ES+) *m/z* 503 $(M+H)^+$, 1005 $(2M + H)^+$.

118

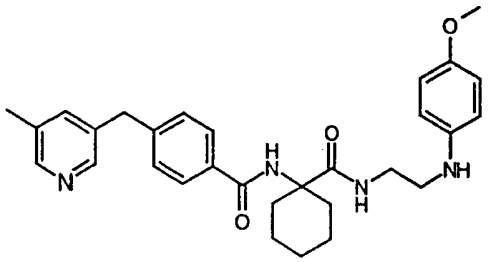


IR (KBr) ν max: 3373, 3346, 3310, 2956, 1656, 1636, 1608, 1528, 1485, 1271, 1237, 1028, 813 cm^{-1}.

^{1}H NMR (400 MHz, CD_3SOCD_3) δ: 8.43 (d, 1H, *J* = 8.0 Hz), 8.31 (d, 1H, *J* = 2.8 Hz), 8.07 (t, 1H, *J* = 6.0 Hz), 7.97 (d, 2H, *J* = 8.5 Hz), 7.46 (dd, 1H, *J* = 2.8, 8.5 Hz), 7.34 (d, 1H, *J* = 8.5 Hz), 7.07 (d, 2H, *J* = 8.5 Hz), 6.71 (d, 2H, *J* = 8.8 Hz), 6.54 (d, 2H, *J* = 8.8 Hz), 5.14 (t, 1H, *J* = 6.0 Hz), 4.52-4.41 (m, 1H), 3.64 (s, 3H), 3.23 (dt, 2H, *J* = 6.0, 6.0 Hz), 3.02 (dt, 2H, *J* = 6.0, 6.0 Hz), 2.50 (s, 3H), 1.75-1.49 (m, 3H), 0.91 (d, 3H, *J* = 6.0 Hz), 0.87 (d, 3H, *J* = 6.0 Hz).

MS (ES+) *m/z* 491 $(M+H)^+$, 981 $(2M+H)^+$.

119

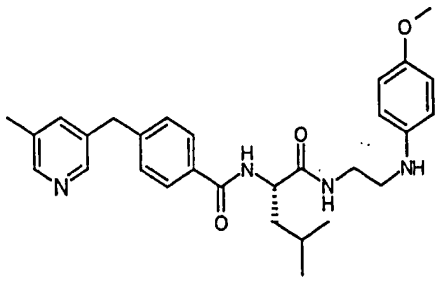


IR (KBr) ν max: 3324, 2930, 2854, 1647, 1513, 1443, 1421, 1296, 1237, 1041, 818, 733 cm^{-1}.

^{1}H NMR (400 MHz, CD_3SOCD_3) δ: 8.33 (s, 1H), 8.26 (s, 1H), 7.84 (s, 1H), 7.81 (d, 2H, *J* = 8.0 Hz), 7.57 (partially resolved t, 1H), 7.45 (s, 1H), 7.36 (d, 2H, *J* = 8.0 Hz), 6.68 (d, 2H, *J* = 9.0 Hz), 6.50 (d, 2H, *J* = 9.0 Hz), 5.04-4.93 (br s, 1H), 4.0 (s, 2H), 3.63 (s, 3H), 3.26-3.15 (partially resolved dt, 2H), 3.02-2.92 (partially resolved dt, 2H), 2.25 (s, 3H), 2.19-2.07 (m, 2H), 1.70-1.65 (m, 2H), 1.60-1.42 (m, 5H), 1.32-1.13 (m, 1H).

MS (ES+) *m/z* 501 $(M+H)^+$.

120

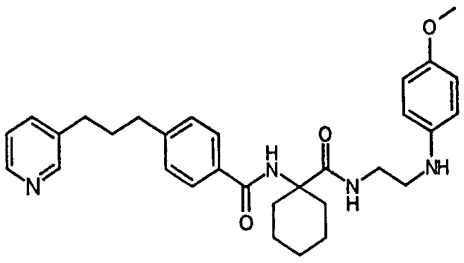


IR (film) ν max: 3295, 2955, 2869, 1634, 1513, 1465, 1440, 1236, 1176, 1134, 1033, 820, 712 cm^{-1}.

^1H NMR (400 MHz, CD_3SOCD_3) δ: 8.39 (d, 1H, *J* = 8.0 Hz), 8.33 (s, 1H), 8.27 (s, 1H), 8.05 (partially resolved t, 1H), 7.86 (d, 2H, *J* = 8.0 Hz), 7.45 (s, 1H), 7.36 (d, 2H, *J* = 8.0 Hz), 6.71 (d, 2H, *J* = 8.5 Hz), 6.54 (d, 2H, *J* = 8.5 Hz), 5.14 (partially resolved t, 1H), 4.52-4.42 (m, 1H), 4.0 (s, 2H), 3.63 (s, 3H), 3.26-3.17 (partially resolved dt, 2H), 3.07-2.94 (partially resolved dt, 2H), 2.25 (s, 3H), 1.73-1.47 (m, 3H), 0.90 (d, 3H, *J* = 6.0 Hz), 0.86 (d, 3H, *J* = 6.0 Hz).

MS (ES+) *m/z* 489 $(M+H)^+$.

121



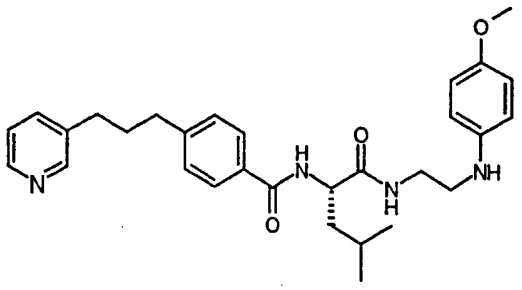
IR (KBr) ν max: 3347, 2931, 2856, 1647, 1512, 1295, 1238, 1039, 822, 714 cm^{-1}.

^1H NMR (400 MHz, CD_3SOCD_3) δ: 8.45 (s, 1H), 8.42 (d, 1H, *J* = 4.5 Hz), 7.85 (s, 1H), 7.82 (d, 2H, *J* = 8.0 Hz), 7.65 (d, 1H, *J* = 8.0 Hz), 7.58 (t, 1H, *J* = 6.0 Hz), 7.37-7.27 (m, 3H), 6.69 (d,

2H, J = 8.5 Hz), 6.51 (d, 2H, J = 8.5 Hz), 5.0 (t, 1H, J = 6.0 Hz), 3.62 (s, 3H), 3.22 (dt, 2H, J = 6.0, 6.0 Hz), 2.98 (dt, 2H, J = 6.0, 6.0 Hz), 2.68 (t, 2H, J = 7.5 Hz), 2.63 (t, 2H, J = 7.5 Hz), 2.19-2.07 (m, 2H), 1.92 (quin, 2H, J = 7.5 Hz), 1.80-1.68 (m, 2H), 1.62-1.43 (m, 5H), 1.32-1.18 (m, 1H).

MS (ES+) *m/z* 515 $(M+H)^+$, 537 $(M+Na)^+$.

122

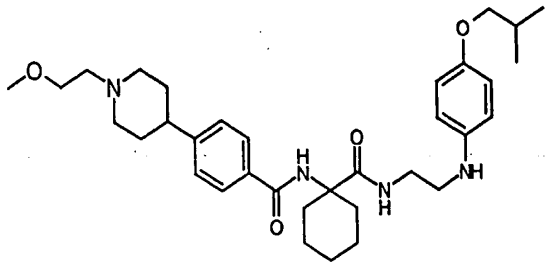


IR (KBr) ν max: 3379, 3323, 2951, 1657, 1629, 1522, 1329, 1280, 1236, 818, 715 cm^{-1}.

^1H NMR (400 MHz, CD_3SOCD_3) δ: 8.45 (s, 1H), 8.42 (d, 1H, J = 4.8 Hz), 8.38 (d, 1H, J = 8.0 Hz), 8.06 (t, 1H, J = 6.0 Hz), 7.86 (d, 2H, J = 8.0 Hz), 7.65 (d, 1H, J = 8.0 Hz), 7.35-7.28 (m, 3H), 6.71 (d, 2H, J = 9.0 Hz), 6.54 (d, 2H, J = 9.0 Hz), 5.14 (t, 1H, J = 6.0 Hz), 4.53-4.43 (m, 1H), 3.63 (s, 3H), 3.23 (dt, 2H, J = 6.0, 6.0 Hz), 3.02 (dt, 2H, J = 6.0, 6.0 Hz), 2.68 (t, 2H, J = 7.5 Hz), 2.63 (t, 2H, J = 7.5 Hz), 1.93 (quin, 2H, J = 7.5 Hz), 1.76-1.47 (m, 3H), 0.91 (d, 3H, J = 6.3 Hz), 0.87 (d, 3H, J = 6.3 Hz).

MS (ES+) *m/z* 503 $(M+H)^+$.

123

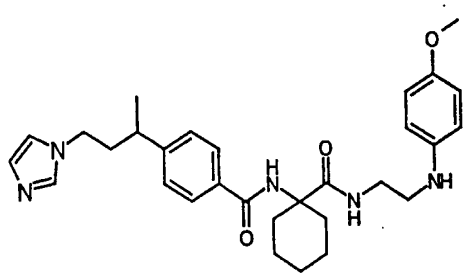


IR (KBr) ν max: 3337, 2933, 2856, 1651, 1513, 1470, 1298, 1233, 1118, 1039, 853, 818 cm^{-1}.

^1H NMR (400 MHz, CD_3SOCD_3) δ: 7.86-7.70 (m, 4H), 7.56 (t, 1H, *J* = 6.0 Hz), 7.34 (d, 2H, *J* = 8.0 Hz), 6.68 (d, 2H, *J* = 8.5 Hz), 6.49 (d, 2H, *J* = 8.5 Hz), 4.96 (t, 1H, *J* = 6.0 Hz), 3.60 (d, 2H, *J* = 6.5 Hz), 3.46 (t, 2H, *J* = 6.0 Hz), 3.26 (s, 3H), 3.21 (dt, 2H, *J* = 6.0, 6.0 Hz), 3.06-2.92 (m, 4H), 2.19-2.07 (m, 3H), 2.02-1.88 (m, 1H), 1.80-1.60 (m, 6H), 1.60-1.43 (m, 5H), 1.32-1.18 (m, 1H), 0.95 (d, 6H, *J* = 6.5 Hz).

MS (ES+) *m/z* 567 $(M+H)^+$.

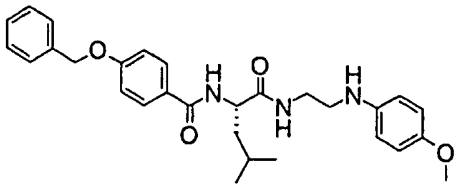
124



^1H NMR (300 MHz, CD_3SOCD_3) δ: 7.86-7.70 (m, 4H), 7.57 (t, 1H, *J* = 6.0 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 7.26 (s, 1H), 6.95 (s, 1H), 6.66 (d, 2H, *J* = 8.5 Hz), 6.49 (d, 2H, *J* = 8.5 Hz), 3.97-3.80 (m, 2H), 3.60 (s, 3H), 3.23-3.05 (m, 2H), 3.0-2.84 (m, 2H), 2.74-2.60 (m, 1H), 2.20-2.0 (m, 4H), 1.80-1.39 (m, 7H), 1.32-1.10 (m, 4H, includes a 3H-d at δ 1.20).

MS (ES+) *m/z* 518 $(M+H)^+$, 540 $(M+Na)^+$, 573 $(M+CH_3CN+H)^+$.

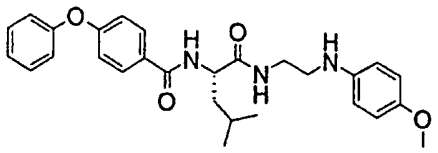
125



mp: 174- 175°C.

MS (ES+): 490 $(M+H)^+$.

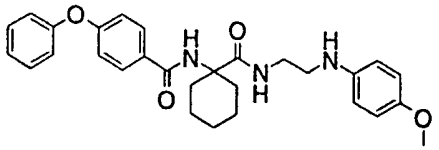
126



mp: 144- 145°C.

MS (ES+): 476 $(M+H)^+$.

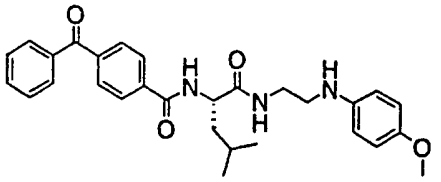
127



mp: 154- 155°C.

MS (ES+): 488 $(M+H)^+$.

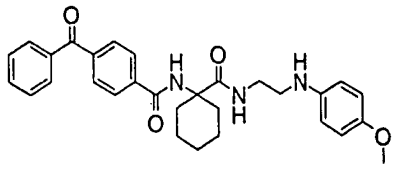
128



^{1}H-NMR (400 MHz, DMSO-d6) δ: 8.69 (d, 1H), 8.10 (t, 1H), 8.08 (d, 2H), 7.79- 7.50 (m, 9H), 6.70 (d, 2H), 6.50 (d, 2H), 5.13 (m, 1H), 4.51 (m, 1H), 3.60 (s, 3H), 3.20 (m, 2H), 3.00 (m, 2H), 1.72 – 1.48 (m, 3H), 0.88 (m, 6H).

MS (ES+): 488 $(M+H)^+$.

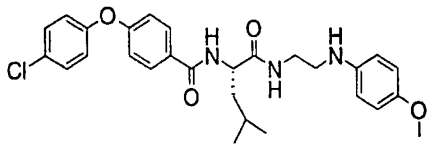
129



^{1}H-NMR (400 MHz, DMSO-d6) δ: 8.14 (s, 1H), 8.0 (d, 2H), 7.79 – 7.55 (m, 8H), 6.68 (d, 2H), 6.49 (d, 2H), 4.99 (t, 1H), 3.60 (s, 3H), 3.21 (m, 2H), 2.96 (m, 2H), 2.18 – 1.21 (m, 10H).

MS (ES+): 500 $(M+H)^+$.

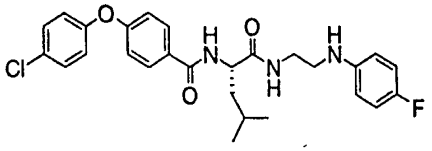
130



mp: 164- 165°C.

MS (ES+): 411 $(M+H)^+$.

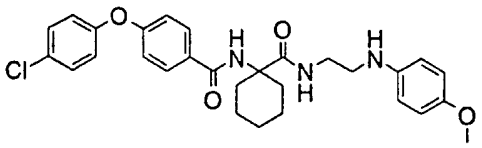
131



mp: 171- 173°C.

MS (ES+): 499 $(M+H)^+$.

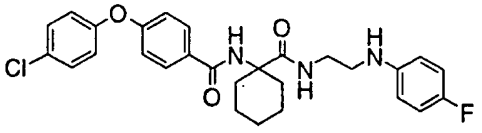
132



mp: 173- 175°C.

MS (ES+): 523 $(M+H)^+$.

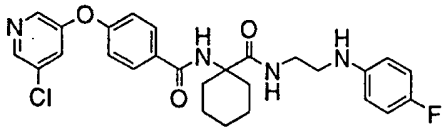
133



mp: 188- 189°C.

MS (ES+): 511 $(M+H)^+$.

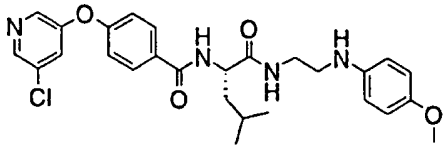
134



mp: 187- 189°C.

MS (ES+): 512$(M+H)^+$.

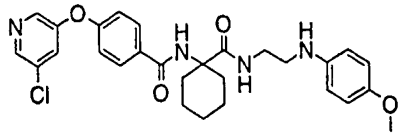
135



mp: 142- 143°C.

MS (ES+): 512 $(M+H)^+$.

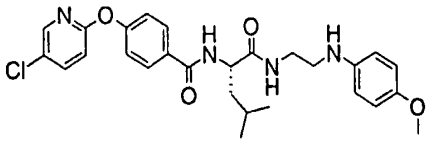
136



mp: 176- 179°C.

MS (ES+): 511 $(M+H)^+$.

137



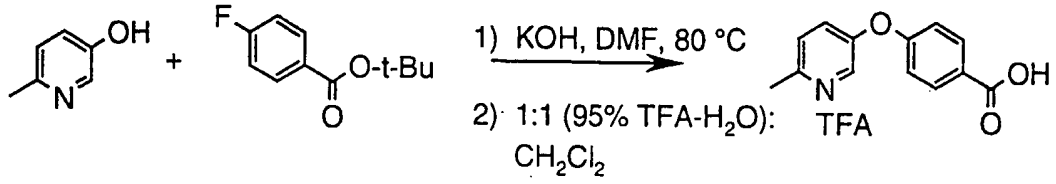
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.12 (m, 1H), 7.81 (d, 2H), 7.68 (m, 1H), 7.17 (d, 2H), 6.93 (d, 1H), 6.75 (d, 2H), 6.69 (m, 2H), 6.58 (d, 2H), 4.64 (m, 1H), 3.72 (s, 3H), 3.48 (m, 2H), 3.24 (m, 2H), 1.81 – 1.64 (m, 3H), 0.97 (m, 6H).

MS (ES+): 512$(M+H)^+$.

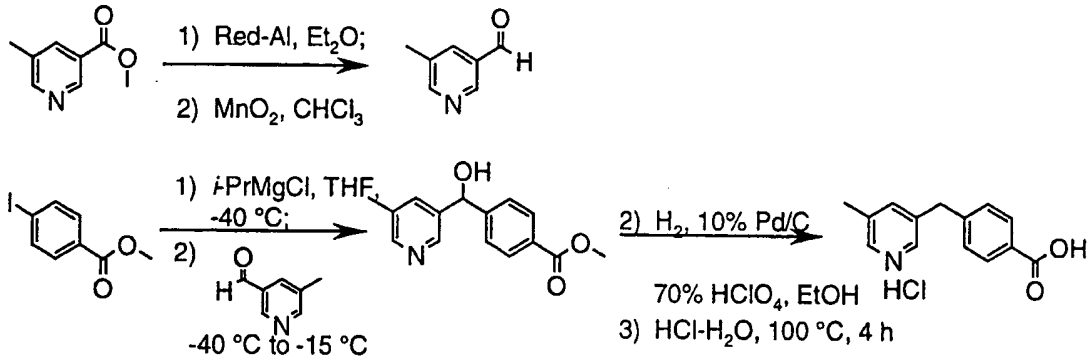
Synthesis of Selected Carboxylic Acid Derivatives

The 4-substituted benzoic acid derivatives are prepared as follows:
Synthetic Schemes:

Scheme A:

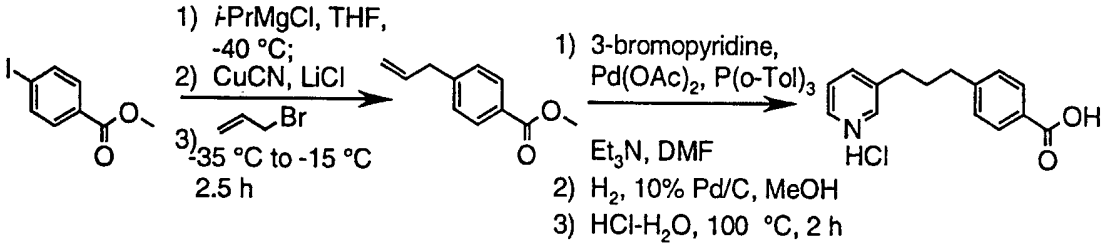


Scheme B:

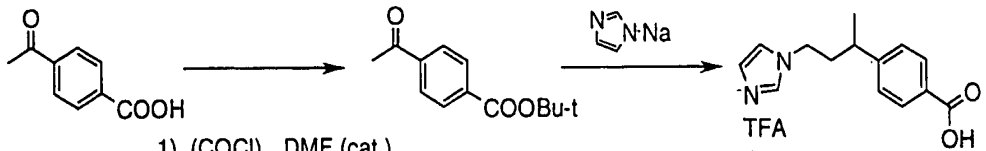


Red-Al = $[(CH_3OCH_2CH_2O)_2AlH_2]Na$

Scheme C:



Scheme D:



1) $(COCl)_2$, DMF (cat.)
Toluene

2) *t*-BuOH, DMAP,
Pyridine

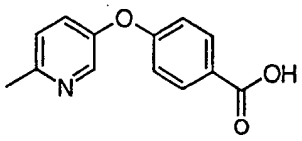
1) *Chem. Pharm. Bull.* **1995**, 43, 829.

2) , DMF

3) 95:5 TFA:H_2O
in CH_2Cl_2

Experimental Procedure:

Synthesis of 4-(6-methyl-pyridin-3-yloxy)-benzoic acid.

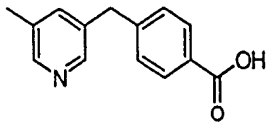


To a solution of 6-methyl-pyridin-3-ol (10 g, 91.6 mmol) in DMF (300 mL) are added KOH pellets (8.3 g, 147.9 mmol). The resultant mixture is heated to 80 °C and stirred at this temperature for 0.5 h. A solution of *tert*-butyl-4-fluorobenzoate (17.9 g, 91.2 mmol) in DMF (100 mL) is then added to the reaction mixture and stirring at 80 °C is continued for 18 h. The mixture is allowed to cool to r.t. and the solvent is removed *in vacuo*. The residue is taken into water and extracted with EtOAc (2 x). The combined organic layers are dried (Na_2SO_4) and the solvent is removed *in vacuo*. The residue is purified by flash chromatography (AcOEt:hexanes 1:10) to afford 4-(6-methyl-pyridin-3-yloxy)-benzoic acid *tert*-butyl ester as an oil. ^{1}H NMR (400 MHz, CD_3SOCD_3) δ: 8.31 (d, 1H, J = 2.8 Hz), 7.91 (d, 2H, J = 8.7 Hz), 7.47 (dd, 1H, J = 2.8, 8.7 Hz), 7.34 (d, 1H, J = 8.5 Hz), 7.06 (d, 2H, J = 8.7 Hz), 2.49 (s, 3H), 1.53 (s, 9H).

4-(6-Methyl-pyridin-3-yloxy)-benzoic acid *tert*-butyl ester (5 g, 17.5 mmol) in CH_2Cl_2 (40 mL) is treated with 95% TFA in H_2O (40 mL). After stirring the mixture at r.t. for 0.5 h, the solvent is removed *in vacuo* and the residue s crystallized in Et_2O to furnish the title compound as a white solid. ^{1}H NMR (400 MHz, CD_3SOCD_3) δ: 8.47 (d, 1H, J = 2.7 Hz), 7.98 (d, 2H, J = 8.7 Hz), 7.71 (dd, 1H, J = 2.7, 8.5 Hz), 7.51 (d, 1H, J = 8.5 Hz), 7.10 (d, 2H, J = 8.7 Hz), 2.55 (s, 3H).

MS (ES-) *m/z* 228 $(M-H)^-$.

Synthesis of 4-(5-methyl-pyridin-3-ylmethyl)-benzoic acid.



(5-Methyl-pyridin-3-yl)-methanol is prepared by reduction of methyl 5-methylnicotinate with sodium bis(2-methoxyethoxy)aluminum hydride at r.t. in a manner similar to that described in the literature (Nishikawa, Y; Shindo, T.; Ishii, K.; Nakamura, H.; Kon, T.; Uno, H. *J. Med. Chem.* **1989**, *32*, 583-593.)

(5-Methyl-pyridin-3-yl)-methanol (450 mg, 3.65 mmol) is then treated with MnO_2 (90%, 3.52 g, 36.5 mmol) in $CHCl_3$ (10 mL) at 65 °C for 2 h. Filtration of the cooled reaction mixture through Celite followed by removal of the solvent *in vacuo* yields 5-methyl-3-pyridinecarbaldehyde as a mixture of the aldehyde and of its hydrate. The mixture is refluxed in toluene under Dean-Stark conditions prior to use. The solvent is removed *in vacuo* and the aldehyde, kept under N_2, is used directly in the next step.

The preparation of 4-(5-methyl-pyridin-3-ylmethyl)-benzoic acid methyl ester is based on a literature procedure describing the synthesis of 4-(hydroxy-phenyl-methyl)-benzoic acid ethyl ester (Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 1701.)

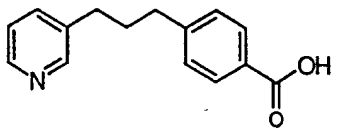
To a solution of methyl 4-iodobenzoate (432 mg, 1.65 mmol) in anhydrous THF (8 mL) at –40 °C is added dropwise a solution of *i*-PrMgCl (2M in THF, 1.4 mL, 2.8 mmol). After stirring the reaction mixture at –40 °C for 2 h, a solution of 5-methyl-3-pyridinecarbaldehyde (200 mg, 1.65 mmol) in THF (5 mL) is added. The reaction mixture is then allowed to warm up slowly from –40 °C to –15 °C over a period of 2.5 h. The solution is poured into sat. aq. NH_4Cl and extracted with EtOAc. The organic layer is washed with brine, dried (Na_2SO_4) and the solvent is removed *in vacuo*. The residue is purified by flash chromatography (19:1 CH_2Cl_2:MeOH) to yield the desired adduct as an oil.

A mixture of 4-[hydroxy-(5-methyl-pyridin-3-yl)-methyl]-benzoic acid methyl ester (310 mg, 1.2 mmol), 70% aq $HClO_4$ (0.200 mL) and 10% Pd/C (150 mg) in EtOH (8 mL) is shaken under an atmosphere of H_2 (4 bar) at r.t. for 4 h. The suspension is filtered over Celite, and the solvent is removed *in vacuo*. The residue is taken into EtOAc-sat. aq. $NaHCO_3$. The layers are separated and the organic phase is washed with brine, dried (Na_2SO_4), and the solvent is removed. The residue is purified by flash chromatography (4:1 hexanes:EtOAc) to afford 4-(5-methyl-pyridin-3-ylmethyl)-benzoic acid methyl ester as an oil.

A solution of 4-(5-methyl-pyridin-3-ylmethyl)-benzoic acid methyl ester (40 mg, 0.166 mmol) in 1:1 conc. HCl:H_2O (4 mL) is heated to 100 °C for 4 h. The solvents are removed *in vacuo* and the resultant pyridinium salt s crystallized in Et_2O.

MS (ES-) *m/z* 226 $(M-H)^-$.

Synthesis of 4-(3-pyridin-3-yl-propyl)-benzoic acid.



4-Allyl-benzoic acid methyl ester is synthesized by a procedure analogous to that used for the preparation of 4-allyl-benzonitrile. See: Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 1701 and references therein.

A solution of 4-allyl-benzoic acid methyl ester (340 mg, 1.93 mmol), 3-bromopyridine (152 mg, 0.96 mmol), $Pd(OAc)_2$ (4.3 mg, 0.0193 mmol), P(*o*-tol)$_3$ (23.5 mg, 0.0772 mmol) and Et_3N (0.403 mL, 2.89 mmol) in DMF (4 mL) under Ar is heated to 100 °C and stirred at this temperature for 18 h. After cooling down to r.t., the mixture is diluted with Et_2O and filtered over Celite. The solvent is removed *in vacuo* and the residue is purified by flash chromatography (5:1 →1:1 Hexanes:EtOAc) to yield a mixture of isomers which are taken directly into the next

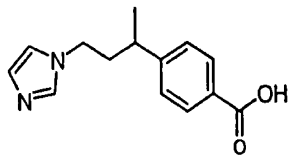
step. The mixture is hydrogenated at r.t. in MeOH (4 mL), in the presence of 10% Pd/C (60 mg) over 2 h to furnish 4-(3-pyridin-3-yl-propyl)-benzoic acid methyl ester as the major compound of an 11:1 mixture of isomers which are separated at a later stage (after coupling with the amine partner).

4-(3-Pyridin-3-yl-propyl)-benzoic acid methyl ester is hydrolyzed by treatment with 1:1 conc. HCl:H_2O (10 mL) at 100 °C for 2 h. The solvents are removed *in vacuo* to provide 4-(3-pyridin-3-yl-propyl)-benzoic acid as its HCl salt.

^{1}H NMR (400 MHz, CD_3SOCD_3) δ: 8.83 (s, 1H), 8.76 (d, 1H, J = 5.5 Hz), 8.44 (d, 1H, J = 8.0 Hz), 7.95 (dd, 1H, J = 5.5, 8.0 Hz), 7.88 (d, 2H, J = 8.0 Hz), 7.36 (d, 2H, J = 8.0 Hz), 2.83 (t, 2H, J = 7.5 Hz), 2.72 (t, 2H, J = 7.5 Hz), 2.0 (quin, 2H, J = 7.5 Hz).

MS (ES-) *m/z* 240 $(M-H)^-$.

Synthesis of 4-(3-imidazol-1-yl-1-methyl-propyl)-benzoic acid.



To a solution of 4-acetylbenzoic acid (5.0 g, 30.5 mmol) in toluene (120 mL) are added $(COCl)_2$ (5.2 mL, 59.6 mmol) and DMF (0.5 mL). The resultant mixture is stirred at room temperature for 1 h. The solvent is then removed *in vacuo* and the resultant solid is used directly in the next step.

To a solution of acid chloride (30.5 mmol) in pyridine (24.6 mL) are added DMAP (cat. amount) and *tert*-BuOH (7.2 mL, 75.3 mmol). After stirring the reaction mixture at r.t. for 3 h, the solution is diluted with Et_2O and washed with aq 1N HCl. The aqueous phase is further extracted with Et_2O. The combined organic layers are washed with 2N NaOH and brine. The organic phase is dried (Na_2SO_4), and the solvent is removed *in vacuo* to provide 4-acetylbenzoic acid *tert*-butyl ester as a crude product which is used directly in the following step. ^{1}H NMR (300 MHz,

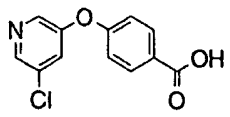
CD_3SOCD_3) δ: 8.11-7.50 (m, 4H), 2.6 (s, 3H), 1.54 (s, 9H).

4-(3-Iodo-1-methyl-propyl)-benzoic acid *tert*-butyl ester is prepared from *tert*-butyl 4-acetylbenzoate according to the literature procedure of Nomura et al. (Kotake, Y; Okauchi, T; Iijima, A.; Yoshimatsu, K.; Nomura, H. *Chem. Pharm. Bull.* **1995**, *43*, 829).

A mixture of 4-(3-iodo-1-methyl-propyl)-benzoic acid *tert*-butyl ester (450 mg, 1.25 mmol) and imidazolyl sodium (135 mg, 1.5 mmol) in DMF (8 mL) is stirred at r.t for 5 h. The solvent is then removed *in vacuo*. A solution of the resultant compound in CH_2Cl_2 (5 mL) is then treated with 95:5 TFA:H_2O (5 mL) for 2 h. After removal of the solvent, 4-(3-imidazol-1-yl-1-methyl-propyl)benzoic acid·TFA is used directly without further purification. ^{1}H NMR (300 MHz, CD_3OD) δ: 8.80 (s, 1H), 7.97 (d, 2H, J = 8.5 Hz), 7.60 (s, 1H), 7.50 (s, 1H), 7.34 (d, 2H, J = 8.5 Hz), 4.29-4.03 (m, 2H), 2.93-2.77 (m, 1H), 2.35-2.20 (m, 2H), 1.33 (d, 3H).

MS (ES-) *m/z* 243 $(M-H)^-$.

Synthesis of 4-(5-chloro-pyridine-3-yloxy)-benzoic acid



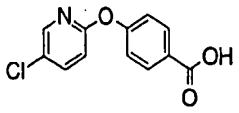
A mixture of 5-chloro-3-pyridinol (2.6g , 20 mmol), 4-fluorobenzoic acid methyl ester (2,6 ml, 20 mmol), 0.5 g 18-Crown-6 and 6.5g 37% w/w potassium fluoride alumina (Preparation according to: E.A. Schmittling, J. Scott Sawyer, Tetrahedron Letters 1991, **32**, 7207) in DMSO (50 ml) is heated at 140°C for 44 hours. The reaction mixture is cooled to room temperature, diluted with ether, and filtered. The resulting solution is placed in a separatory funnel and washed once with water and once with saturated potassium chloride solution. The organic phase is dried (sodium sulfate), filtered, and concentrated in vacuo. The product is purified by flash chromatography on silica gel eluting with toluene/ethanol (85:15).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.39 (m, 1H), 8.32 (m, 1H), 8.08 (d, 2H), 7.37 (m, 1H), 7.06 (d, 2H), 3.91 (s, 3H).

4-(5-chloro-pyridine-3-yloxy)-benzoic acid methyl ester (1.35g, 5.3mmol) is dissolved in 4N HCl (10 ml) and heated to reflux for 4 hours. The reaction mixture is concentrated in vacuo and the product recrystallized from acetone.

mp: 175- 178°C.

MS (ES+): 250 $(M+H)^+$.

Synthesis of 4-(5-chloro-pyridine-2-yloxy)-benzoic acid



A mixture of 2,5-dichloropyridine (2.96 g, 20 mmol), 4-hydroxy benzoic acid ethyl ester (6.64 g, 40 mmol), potassium carbonate (2.77 g, 20 mmol) and copper powder (0.254 g, 4 mmol) is heated for 4 hours at 160°C. The reaction mixture is cooled to room temperature, diluted with ethyl acetate and 50 ml of 2N NaOH is added. The resulting solution is placed in a separatory funnel and washed once with 1N NaOH, once with H_2O and once with saturated sodium chloride solution. The organic phase is dried (sodium sulfate), filtered, and concentrated in vacuo. The product is purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (18:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.15 (m, 1H),), 8.09 (d, 2H), 7.69 (m, 1H), 7.15 (d, 2H), 6.94 (d, 1H), 4.37 (q, 2H), 1.39 (t, 3H).

MS (ES+): 278$(M+H)^+$.

A solution of 4-(5-chloro-pyridine-2-yloxy)-benzoic acid ethyl ester (3.2 g, 11.54 mmol) and 2N NaOH (5.8 ml, 23.08 mmol) in methanol (100 ml) is heated to reflux for 2 hours. The reaction mixture is diluted with H_2O (300 ml) and placed in a separatory funnel. The solution is once extracted with ether and then adjusted to pH 4 with 1N HCl, thereby the product is precipitating as white crystalls.

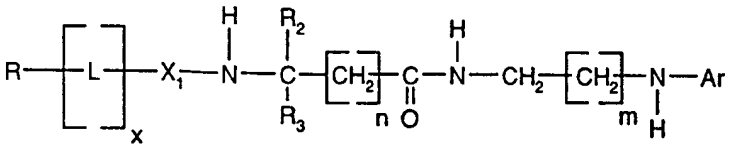
mp: 213- 214°C.

MS (ES+): 250 $(M+H)^+$.

CLAIMS

1. An aminoacid-arylaminoalkylamide in which the C-terminal carboxy group of the amino acid is substituted by an arylaminoalkylamino substituent and in which the amino nitrogen atom of the amino acid forms a peptide or pseudopeptide linkage which optionally additionally comprises a -methylene-hetero atom- linker or an additional hetero atom, through which it is directly substituted by aryl, lower alkyl, lower alkenyl, lower alkynyl or heterocyclyl,
or a physiologically-acceptable and -cleavable ester or a salt thereof.

2. A compound according to claim 1, of formula I, or a physiologically-acceptable and -cleavable ester or a salt thereof



I

wherein:

R is optionally substituted (aryl, lower alkyl, lower alkenyl, lower alkynyl, or heterocyclyl);

R_2 and R_3 are independently hydrogen, or optionally substitued [lower alkyl, cycloalkyl, bicycloalkyl, or (aryl, biaryl, cycloalkyl or bicycloalkyl)-lower alkyl]; or

R_2 and R_3 together represent lower alkylene, optionally interrupted by O, S or NR_6, so as to form a ring with the carbon atom to which they are attached
wherein R_6 is hydrogen, lower alkyl or aryl-lower alkyl; or

either R_2 or R_3 are linked by lower alkylene to the adjacent nitrogen to form a ring;

Ar is optionally substituted aryl;

X_1 is -C(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-P(O)(OR_6)-$

wherein R_6 is as defined above;

L is optionally substituted -Het-, $-Het-CH_2-$ or $-CH_2-Het-$,

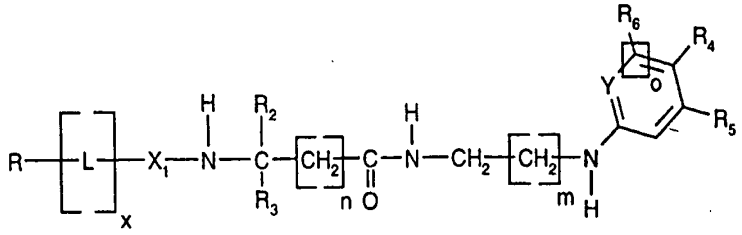
wherein Het is a hetero atom selected from O, N or S;

n is 0 or 1;

m is 1, 2, 3, 4 or 5;

x is 0 or 1.

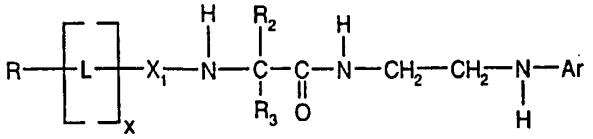
3. A compound according to claim 2 of formula II, or a physiologically-acceptable and -cleavable ester or a salt thereof



II

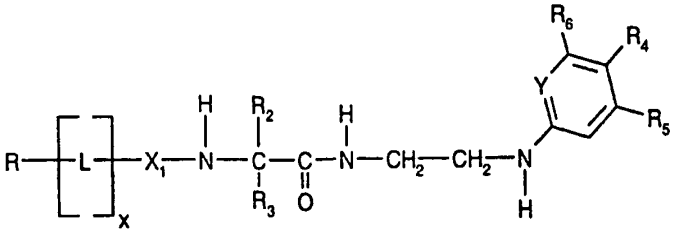
wherein R, R_2, R_3, L, X_1, x, n and m are are as defined in claim 2, and R_4, R_5 and R_6 independently are H, lower alkyl (e.g. methyl), lower alkoxy (e.g. methoxy, ethoxy, isopropoxy, isobutoxy, aryl-lower alkoxy (e.g. -O-benzyl), cycloalkoxy, cycloalkyl-lower alkoxy (e.g. O-methylcycloalkyl), halogen, e.g. Cl, Br or F, or trifluoromethyl.

4. A compound according to claim 1 of formulae I' and II', or physiologically-acceptable and -cleavable esters or salts thereof



I'

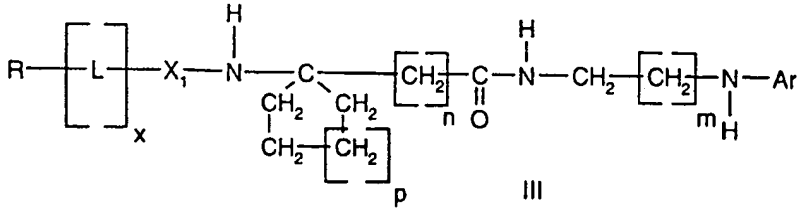
or



II'

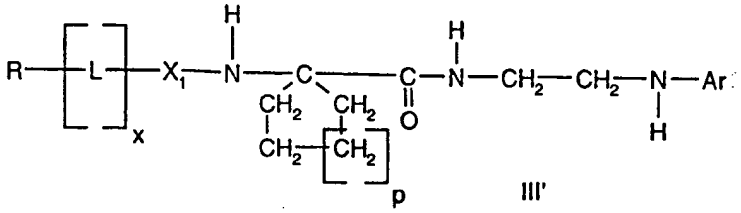
wherein the symbols have meaning as defined in claim 2.

5. A compound according to claim 2 of formula III



III

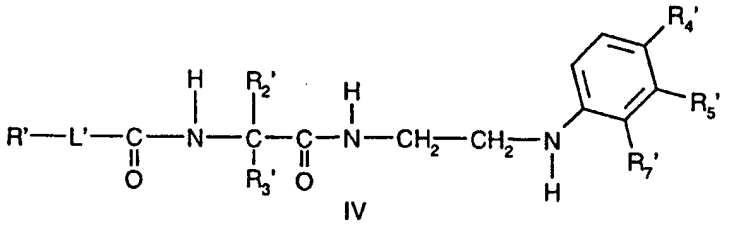
or especially III'



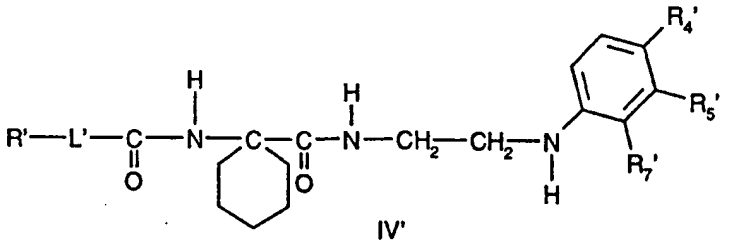
III'

wherein R, L, X_1, Ar, n and m are as defined in claim 2 and p is 1, 2, 3 or 4; or physiologically-acceptable and -cleavable esters or salts thereof (and compounds in which the cycloalkyl group comprises an internal carbon-carbon bond or lower alkylene, e.g. methylene, bridge).

6. A compound according to claim 2 of formulae and IV or IV', or physiologically-acceptable and -cleavable esters or salts thereof



IV



IV'

wherein

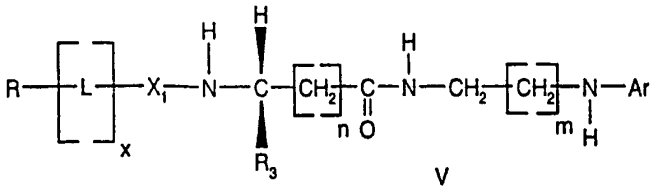
R' is optionally substituted (aryl or heterocyclyl);

L' is $-CH_2-O-$, $-CH_2-$, $-OC(R_{14}R_{15})-$ or a direct bond, where R_{14} and R_{15} are independently H or lower alkyl;

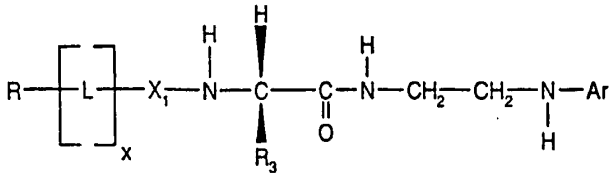
R_2' is H and R_3' is lower alkyl or cycloalkyl; and

R_4', R_5' and R_7' are independently H, halogen, aryl-lower alkoxy, lower alkyl, lower alkoxy, cycloalkyloxy, cycloalkyl-lower alkoxy, heterocyclyloxy, heterocyclyl-lower alkoxy or optionally substituted amino-lower alkoxy.

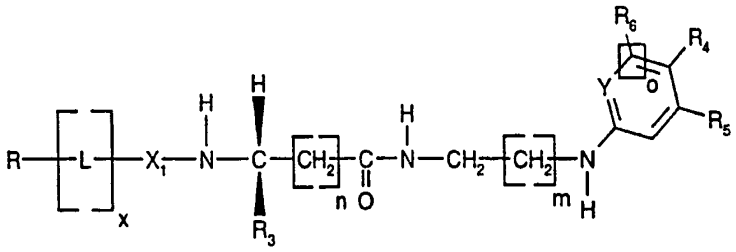
7. A compound according to claim 2 of formula V, V', V", V"' or V""



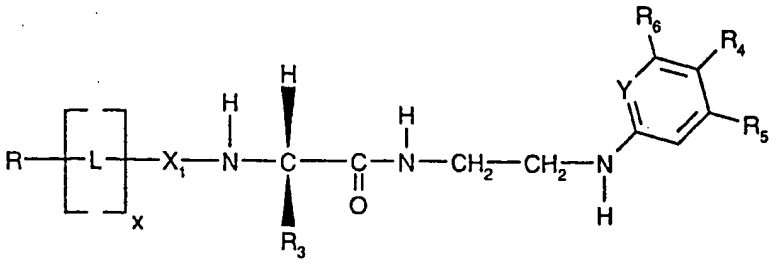
V



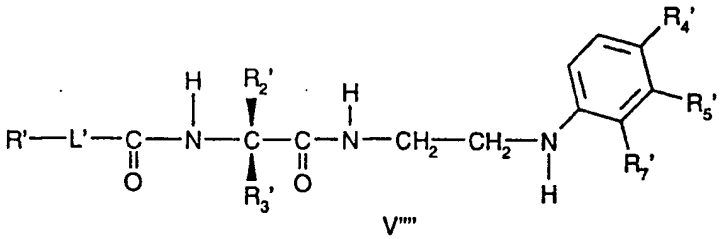
V'



V"



V'''

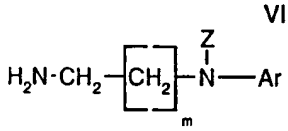


V''''

wherein the symbols are as defined in claim 2 and claim 6, and physiologically-acceptable and -cleavable esters or salts thereof.

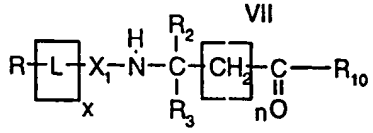
8. A process for the preparation of a compound of formula I as defined in claim 2, comprising

a) reacting a compound of formula VI



VI

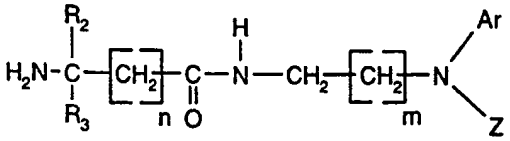
wherein Ar and m are as previously defined and Z is H, an amino protecting group or a solid phase support, with a compound of formula VII



VII

wherein R, R_2, R_3, L, X_1, x and n are as previously defined and R_{10} is OH or a leaving group; or

b) for preparation of a compound of formula I in which $-X_1-$ is -C(O)- and x is 0, reacting a compound of formula VIII



VIII

wherein R_2, R_3, Ar, n and m are as previously defined and Z is H, an amino protecting group or solid phase support, with a compound of formula $RCOR_{10}$, wherein R and R_{10} are as defined above;

and in the above processes, if required, temporarily protecting any interfering reactive groups and then isolating the resulting compound of the invention; and if desired, converting any resulting compound into another compound of the invention; and/or if desired, converting a resulting compound into a salt or ester, or a resulting salt or ester into the free acid or base or into another salt or ester; and if required recovering the resulting product from a solid phase.

9. An aminoacid-arylaminoalkylamide as defined in claim 1, for use as a pharmaceutical; a pharmaceutical composition comprising an aminoacid-arylaminoalkylamide as defined in claim 1 as an active ingredient;
a method of treating a patient suffering from or susceptible to a disease or medical condition in which cathepsin K is implicated, comprising administering an effective amount of an aminoacid-arylaminoalkylamide as defined in claim 1 to the patient; or
use of an aminoacid-arylaminoalkylamide as defined in claim 1 for the preparation of a medicament for therapeutic or prophylactic treatment of a disease or medical condition in which cathepsin K is implicated.

10. An aminoacid-arylaminoalkylamide selected from the compounds of Examples 1-137

INTERNATIONAL SEARCH REPORT

Inte :onal Application No
PCT/EP 00/01197

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C271/22 C07C271/28 C07C237/04 C07D295/112 C07D295/108
C07D295/088 C07D295/03 A61K31/34 A61K31/40 A61P19/02
A61P19/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 09149 A (UNIV NAPIER ;MINCHER DAVID JOHN (GB)) 6 April 1995 (1995-04-06) * see the examples * ---	1
X	WO 94 01771 A (PATCHORNIK ZIPORA ;PATCHORNIK AVRAHAM (IL)) 20 January 1994 (1994-01-20) page 29; table 3 ---	1-7
X	FILIPPOVA, IRINA YU. ET AL: "Fluorogenic peptide substrates for assay of aspartyl proteinases" ANAL. BIOCHEM. (1996), 234(2), 113-18 , XP000907265 page 114 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 May 2000	28/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bader, K

3

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 00/01197

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MORIER-TEISSIER, ELISABETH ET AL: "Synthesis and antitumor properties of an anthraquinone bisubstituted by the copper chelating peptide Gly-Gly-L-His" J. MED. CHEM. (1993), 36(15), 2084-90 , XP002138282 page 2085 page 2088 ---	1
X	NAEGLER, DORIT K. ET AL: "Major Increase in Endopeptidase Activity of Human Cathepsin B upon Removal of Occluding Loop Contacts" BIOCHEMISTRY (1997), 36(41), 12608-12615 , XP000907282 page 1208 ------	1

3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/ 01197

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-9 relate to an extremely large number of possible compounds. In fact, the claims contain so many options that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely claims 1-9 in as far as they relate to the examples 1-137 as depicted in the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/EP 00/01197

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9509149 A	06-04-1995	AT 163404 T	15-03-1998
		AU 7705294 A	18-04-1995
		CA 2172958 A	06-04-1995
		DE 69408683 D	02-04-1998
		DE 69408683 T	01-10-1998
		EP 0721447 A	17-07-1996
		ES 2115977 T	01-07-1998
		JP 9506862 T	08-07-1997
		US 5733880 A	31-03-1998
WO 9401771 A	20-01-1994	IL 102495 A	15-06-1998
		AU 4784493 A	31-01-1994
		EP 0650595 A	03-05-1995
		JP 8505220 T	04-06-1996
		US 5576216 A	19-11-1996